ISSN 1683-0407

ihcp

INSTITUTE FOR HEALTH AND CONSUMER PROTECTION

ACTIVITY REPORT 2002

EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

Report EUR 20660 EN

The IHCP is located in northern Italy, on the lakeshore of Lago Maggiore (Varese province). The nearest city is Milan (approximately 60 km south-east), and the region is served by Malpensa International Airport, located at about 30 km from the JRC.

European Commission
Joint Research Centre (DG JRC)
Institute for Health and Consumer Protection (IHCP)
TP 202
I-21020 Ispra (VA) • Italy

Tel.: + 39 0332 786288
Fax: + 39 0332 789059

E-mail: ihcp-contact@jrc.it
Website: http://ihcp.jrc.cec.eu.int/

Editor
M. Hoffmann

Graphic design and layout
J.J. Blasco & R. Sánchez (cover)
Information and Public Relations Unit • JRC Ispra

EUR Report 20660 EN

ISBN 92-894-5312-5

Printed in Italy

Institute for Health and Consumer Protection

Activity Report 2002

EUROPEAN COMMISSION
JOINT RESEARCH CENTRE


ihp

CONTENTS

Foreword

2002 was a year of significant change for the IHCP. This change brought about a need to further re-focus and align the JRC activities in support of the EU policies, giving the IHCP a key position in the 6th Framework Programme (FP6).

In the frame of this prioritisation exercise, the activities concerning the support in the access to information on medicinal products were successfully finalised with their transfer to EMEA in London and the Competent Authorities of the Member States. Subsequently, the Support to the Pharmaceutical Research Unit (SPR) ceased to exist at the end of 2002.

During the period under review some of the activities of the Food Products Unit (FPU) were transferred to IRMM, whereas the GMO related activities were brought under a new Biotechnology and GMO Unit, which has a prime position in the European Network of GMO Laboratories. The third change relates to the Physical and Chemicals Exposure Unit (PCE), which was created in June 2002 through a combination of existing IHCP activities and projects transferred from the Institute for Environment and Sustainability (IES) and the FPU.

In 2002 the Commission put much effort in developing the Chemical Policy in which our Institute plays a central role. Three out of five scientific Units of the IHCP, namely the Physical and Chemical Exposure Unit (PCE), the European Centre for the Validation of Alternative Methods (ECVAM) and the European Chemicals Bureau (ECB) perform work in direct support of the EU Chemicals Policy. The activities of these three Units are strongly linked to each other, while their roles are very different. The prime role of ECVAM is to co-ordinate and fund (pre)-validation studies while carrying out research in various areas of toxicology relevant to the testing of chemicals. The tasks of the ECB are focused on the scientific and technical support for developing and improving EU chemical policies by evaluating the risks of chemicals to humans and the environment. The PCE Unit hosts a multi-disciplinary team of researches that combine efforts to reduce the existing deficiencies of human exposure data.

Besides its core activities the IHCP has actively contributed in shaping the European Research Area. This has been pursued through extensive networking, such as the European Network of GMO Laboratories, training of scientists from the Member States and Candidate Countries. The interdisciplinary nature of the work carried out is also a key element in the Marie Curie Training Site BIORAD, which is jointly hosted by ECVAM and the Biomedical Materials and Systems Unit (BMS). This site provides high-level interdisciplinary doctoral training in testing of biomaterials using radiotracers.

In conclusion, I would like to thank the staff of the IHCP for the continuous support they provided in making our achievements a valuable contribution to EU policies and European Citizens.

March 2003

Kees Van Leeuwen
IHCP Director

IHCP Mission Statement

The mission of the IHCP is to provide scientific support to the development and implementation of EU policies related to health and consumer protection. The IHCP carries out research to improve the understanding of potential health risks posed by chemicals, biocides, genetically modified organisms, contaminants released from food contact materials and consumer products.

Scientific Objectives

IHCP activities focus on the following scientific objectives:

- Validation of methods to detect genetically modified organisms (GMOs) in food and feed.
- Development and validation of alternative testing methods to replace, reduce or refine the use of laboratory animals in biomedical sciences.
- Assessment of risks to health and environment from chemical substances, and management of related information service.
- Evaluation and quantification of exposure to environmental stressors (such as chemicals, biological contaminants, radiation, and noise).
- Development, validation and use of advanced processing techniques and test methods for the qualification of biocompatible materials, medical devices, and health diagnostics.

End-users/Collaborations

IHCP's direct end-users are services within the European Commission. Moreover, IHCP collaborates with a large number of universities, industrial partners, European and national authorities, international organizations, and consumer associations (the following is a non-exhaustive list):

Customers (within EC)	• DG Agriculture, DG Environment, DG Enterprise, DG Consumer Protection (SANCO), DG Research, DG Trade, DG Taxation and Customs Union (TAXUD), DG Enlargement, European Anti-Fraud Office (OLAF) • DG JRC: EI (Ispra), IRMM (Geel), IAM (Petten), ITU (Karlsruhe), IPTS (Seville) • European Medicine Evaluation Agency (EMEA)
Customers (outside EC)	• European Parliament • International organisations (i.e., OECD, WHO, FAO, Council of Europe, European Directorate for the Quality of Medicines (EDQM)) • Interagency Committee for the Validation of Alternative Methods (ICCVAM) • European agencies - Governments (i.e., Competent authorities responsible for the implementation of biotechnology and novel food Directives; chemical authorities, pharmaceutical regulatory agencies in the European Economic Area (EEA), regulatory and health care authorities) • Non-governmental organisations (NGOs) • Industry (i.e., biotechnology, food and feeding stuff, chemicals, cosmetics, biomedical and pharmaceutical) • Consumer Organisations • National Research Institutions and Universities

Executive Summary

The chemicals industry is one of the most important manufacturing industries in the EU. Chemical sales alone amounted to 488 billion Euro in 2001 and about 3 million people are employed, either directly or indirectly, by the Chemicals Industry in the EU. In February 2001, the Commission, after consultation with all stakeholders including chemical producers, industrial users, citizens' groups and animal welfare organizations, issued a White Paper outlining the chemicals policy strategy. Currently the Commission is in the process of establishing a single review and testing system called REACH (Registration, Evaluation and Authorization of CHemicals) for all existing and new chemicals.

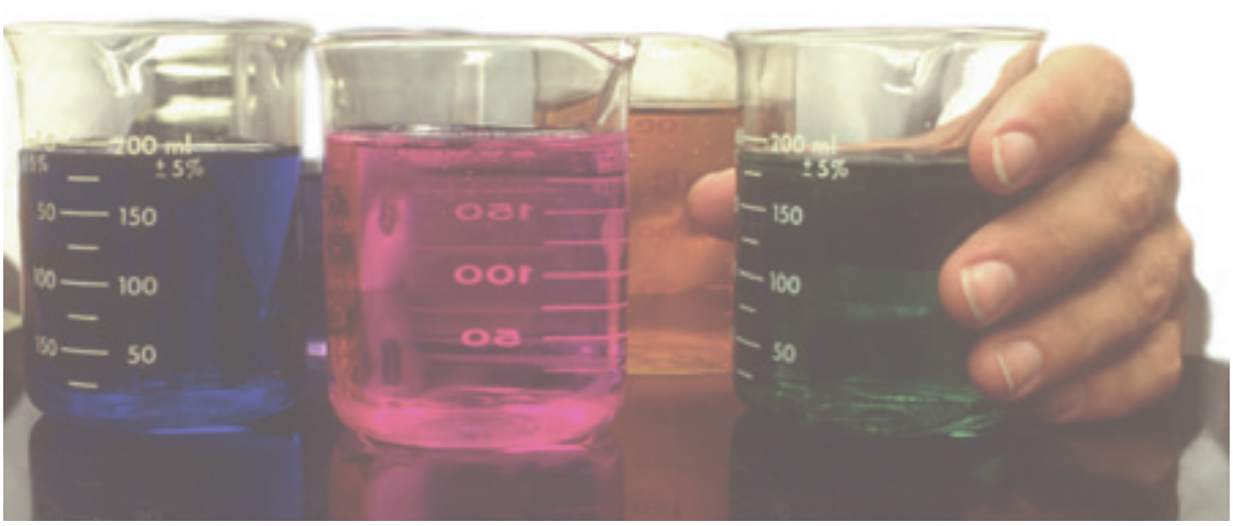
In view of the lack of basic data on industrial chemicals and the fact that more than 100 000 chemicals still have to be tested, the JRC European Chemicals Bureau (ECB) at the Institute for Health and Consumer Protection has continued to put priority on the development and validation of methods for continuous improvement in the prediction and assessment of their risks. The work of ECB is carried out in close collaboration with ECVAM, the European Centre for the Validation of Alternative Methods to animal experiments. ECVAM plays a leading role at the European level in the independent evaluation of the relevance and reliability of tests for specific purposes (i.e. toxicity assessments of various types of chemicals, quality control and safety assessments of biologicals), through research on advanced methods, new test development and validation, and the operation of specialised databases.

To rectify the lack of data on human exposure to physical and chemical stressors, which are relevant for risk assessment analysis, the Physical and Chemical Exposure (PCE) Unit of the IHCP develops methods for improving the monitoring and assessment of human exposure to chemicals. Upon request of DG Health and Consumer Protection a European Information System on Risks of Chemicals release from Products and Articles will be set up (EIS-CHEMRISKS).

Responding to the political and public concerns regarding the use of genetically modified organisms (GMOs) in food and feedstuff, the Biotechnology & GMOs Unit of the IHCP focuses its work on the development and validation of analytical methods for the detection, identification, quantification and traceability of GMOs. This Unit was created on 1st November 2002 after the transfer of the Food Products Unit to IRMM.

In 2002 the Biomedical Materials and Systems (BMS) Unit carried out work characterizing the surface and the release of potentially hazardous substances from medical devices and consumer products and contributed to the development of optical and nuclear imaging techniques. Its surface modification laboratories received international recognition for its activities related to the characterization and modification of interfaces, the improvement of biocompatibility and functionalization of surfaces.

The support to the Pharmaceutical Research (SPR) Unit was stopped in December 2002 after the successful finalization of the transfer of its activities to EMEA and the Competent Authorities of the Member States.



Biotechnology & GMOs Unit

Created in November 2002 the Biotechnology & GMOs Unit is the JRC reference for the provision of scientific and technical support to the EC biotechnology regulatory framework and develops biotechnology expertise in areas relevant for health and consumer protection. Particular focus is on the development and validation of appropriate methods for detection, identification and quantification of genetically modified organisms (GMOs) in different types of matrices. Following a natural collaboration between more than 40 EU and PECO enforcement labs under the chairmanship of IHCP, the European Network of GMO Laboratories (ENGL) has been inaugurated.

In 2002 the Biotechnology & GMOs Unit played a leading role in the QPCRGMOFOOD and the ENTRANSFOOD competitive projects. To complement the activities, the Unit has decided to embark the INFORMALL concerted action project, the kick off of which is planned for 2003.

European Centre for the Validation of Alternative Methods (ECVAM)

ECVAM plays a key role in the implementation of the New EU Chemicals Policy in order to minimise the use of experimental animals and to speed up the policy implementation throughout the development and validation of more cost-effective and faster *in vitro* techniques. ECVAM has established an ad-hoc Working group on Chemicals with the ultimate goal to propose a strategy on the development and validation of new alternative (non-animal) methods. To best achieve this objective ECVAM organised several meetings of this working group and its subgroups in 2002, which resulted in the publication of a comprehensive report, which formed the basis for the establishment of project management groups for all areas of chemical safety testing and the initiation of a fund of the chemicals industry.

At the same time, ECVAM has initiated, continued or finalised various (pre)validation studies, such as the ECVAM/ ICCVAM (US Interagency Coordinating Committee for the Validation of Alternative Methods) validation study on acute systemic toxicity, studies for metabolism-mediated toxicity, nephrotoxicity and skin irritation testing, as well as in the area of biologicals. In this context, four cell-based tests successfully passed the multi-partner validation project on monitoring side effects, such as fever reactions, arising from contaminants of injectable drugs. The ECVAM Scientific Advisory Committee issued 6 final statements, this year: three on the scientific validity of *in vitro* methods for embryotoxicity testing as a follow-up of their endorsements in 2001 and three on potency testing and quality control of vaccines.

In line with its institutional duties, the year 2002 has seen the consolidation of ECVAM's scientific information service (SIS) that reached 1500 active registered users to its databases providing factual and evaluated (ready-to-use) information on advanced alternative methods for toxicology assessments, and ECVAM established a comprehensive web site about all major activities of the whole Unit.

ECVAM, moreover, continued to extend its laboratory facilities, e.g. with a microarray technology for toxicogenomics, i.e. the analysis of gene expressions due to exposure to xenobiotics, which might lead to a second generation of alternative methods to animal models.

A major event for ECVAM in 2002 was the Status Seminar held in Ispra from 4th to 6th of June 2002 with participation of stakeholders and main collaborators of the Unit, in addition to the ECVAM and IHCP staff. Furthermore, the year 2002 brought changes with regard to ECVAM's leadership. Dr. Thomas Hartung was appointed as new Head of Unit after the retirement of Prof. Michael Balls.

European Chemicals Bureau (ECB)

The ECB plays a central role in the establishment of the New EU Chemicals policy. It is responsible for the technical and scientific work needed for the development, introduction, and adaptation to technical progress of testing methods of Annex V to Directive 67/548/EEC.

The web page for Biocides, **http://ecb.jrc.it/biocides**, has continuously been updated, to enable industry to check that their information is registered correctly and to distribute information to third parties.

The ECB has been engaged in two research activities in 2002:

- The OMNIITOX project (Operational Models aNd Information tools for Industrial applications of eco/TOXicological impact assessments) aiming at the enhancement of the capability of industry to select more environmentally benign chemicals and processes. The main activity in 2002 has been an LCA case study, comparing application of metal working fluids with and without chlorinated paraffins.

- The promotion of the development, validation and implementation of (Q)SARs, (quantitative) structure-activity relationships, which will be useful for regulatory purposes, in particular on the needs of the future EU legislation on chemicals (REACH system). The work is performed in close collaboration with ECVAM.

Physical and Chemical Exposure (PCE)

In order to overcome the methodological and data deficiencies on human exposure, which represent a major bottleneck in the risk assessment analysis, the Physical and Chemical Exposure Unit of the IHCP is developing methods for improving the characterisation of human exposure to chemicals and physical stressors. The Unit was created in June 2002 after the transfer of some selected activities from IES to the IHCP.

The UNIE Project (UV-radiation, Noise, Indoor Exposure, Electromagnetic Fields) investigates the health risk of European citizens from the exposure to environmental stressors, including chemicals, biological contaminants, UV-radiation and electromagnetic fields.

The UV laboratory provides support to specific policy actions on UV and hosts the European Reference Centre for UV Radiation Measurements (ECUV). In the context of the HARMONOISE project ("Harmonised, Accurate and Reliable Methods for the EU Directive on the Assessment and Management of Environmental Noise") the first measurement campaign to collect noise & micrometeorological data, needed for the validation of the harmonised model under development, was successfully performed in 2002.

In the frame of the project PICADA the photo-catalytic activity of TiO_2, added to different building materials (concrete etc.) has been tested for its ability to induce degradation of inorganic (NO, NO_2, O_3) and organic compounds (VOCs) using the INDOORTRON facility.

With the participation of DG SANCO two main projects (EIS-CHEMRISKS and CHEM-TEST) have been formulated and approved as European-wide networks to systematically exchange and assess information on emerging issues related to "Risks from chemicals released from consumer products and articles".

The Unit has promoted a European Information System on public health protection issues related to Electromagnetic fields (EIS-EMF) as a common basis for decision makers to increase the coherence of the approaches taken in the various Member States and help restore public confidence. In December 2002 the kick-off meeting of the project INDEX (Indoor Exposure Limits) was organised. The aim of the project is to create a network of European leading scientists in the area of indoor air pollution and the herewith associated health impacts in order to identify priorities and assess the need for a Community strategy and action plan for the establishment of indoor exposure limits for priority pollutants. The INDEX project is financially supported by DG SANCO.

The activities in the area of toxicology focused on the development of toxicogenomic approach in assessing the exposure to environmental chemicals and chemical mixtures. Studies were carried out applying DNA microarrays techniques to assess gene expression modulation following exposure to chemical stressors.

Activities in 2002 of the contact materials laboratories included pre-normative research (migration into dry foods, active packaging, reaction products from jar sealants, release of chemicals from toys) and monitoring of contaminants (from toys and in baby foods). Two large conferences on recyclability and on scientific mobility and one course of mathematic modeling were organized. The activities in 2002 have resulted in two milestones: the designation of the contact materials laboratories as a future Community Reference Laboratory by DG SANCO, endorsed by the request of Member States to lead and co-ordinate an Official Network of Enforcement Laboratories. Another milestone has been the procedure of accreditation of the laboratory, which has resulted in an ISO 17025 Accreditation in January 2003.

The institutional work of BEVABS included aspects regarding training within the frame of the new official laboratories and quality control of isotopic measurements for wines. A new competitive project WINE-DB involving the network of laboratories of the EU Wine Data bank, and new partners from candidate countries (Hungary, Czech Republic, Croatia and Romania) started in May 2002.

Biomedical Materials and Systems (BMS)

The Biomedical Materials and System (BMS) Unit develops, validates and uses advanced processing techniques and test methodologies for the qualification of biocompatible materials, medical devices, and diagnostic systems including medical applications of nuclear technology.

The research activities in 2002 in the BMS Unit were executed in two institutional projects, "Reliability of Medical Devices (REMED)" and "Minimally Invasive Medical Systems (MIMES)", focussing on the following key areas:

- Surface technology for hybrid bio-interfaces and surface analysis for contamination of medical devices.
- Release assessment of biomedical and orthopaedic implants including performance testing of hip and knee implants.

- Biomechanical characterisation of calcified tissues and interfaces.
- Optical and nuclear imaging techniques for cancer diagnosis.

In the area of surface technology, the aim of the R&D program is to develop, assess and test plasma surface treatment for biomedical applications. In particular, progress has been made in the deposition of carbon-based materials for prosthetic applications and on the functionalisation of surfaces to improve properties such as adhesive bonding, wettability and biocompatibility. Another focus of research in 2002 was on the applications of plasma sources for the sterilization of medical devices using plasma processes for the destruction of spores and pyrogens in medical devices and polymer treatment for pharmaceutical packaging.

The set-up of the laboratory for testing of orthopaedic implants has been completed with a new hip and knee simulator which complements the existing equipment for wear release testing. The laboratory covers the whole range of testing facilities from screening tests to most advanced tests simulating the mechanical loading under actual conditions.

In the area of optical imaging, work has continued on the development of endoscopic fluorescence based methods for tissue characterisation, while further progress has been made in the development of optical fibre based sensors for monitoring temperature profiles over extended areas for application in the treatment of tumours.

In 2002 the contract for the joint ECVAM-BMS Unit Marie Curie Training Site "Research Training in Biomaterials Testing Using Radiotracers" (BIORAD) have been signed and first students have been selected. BIORAD aims at providing high-level interdisciplinary doctoral training in testing of biomaterials using radiotracers. A key facility for this Training Site is the IHCP Biocyclotron, which is a concept that includes an interdisciplinary team of scientists working in an infrastructure of a cyclotron, laboratories for both the safe handling of radioisotopes and their use in biological and toxicological studies.

The BMS Unit manages two Thematic Networks and participates in six Shared Cost Actions.

Support to Pharmaceutical Research (SPR)

The SPR Unit has developed several complementary information and communication systems aiming at assisting the access to the authorised information on medicinal products throughout the EU regulatory authorities. In particular:

- The EudraNet Services supporting the cooperation for the entire EU market and post marketing surveillance.
- The EudraTrack System supporting the marketing authorisation process of medicinal products through the mutual recognition procedure enforced by the Council Regulation (EEC) No. 2309/93 and by Directive 2001/82/EC and Directive 2001/83/EC.

During 2002 the SPR Unit successfully finalized the transfer of the EudraNet Services to the EMEA and the services of the EudraTrack System to the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) regulatory authority.

The Head of the SPR Unit F. Argentesi retired on 31 July 2002. The SPR Unit ceased to exist at the end of 2002.

The IHCP in Figures–2002

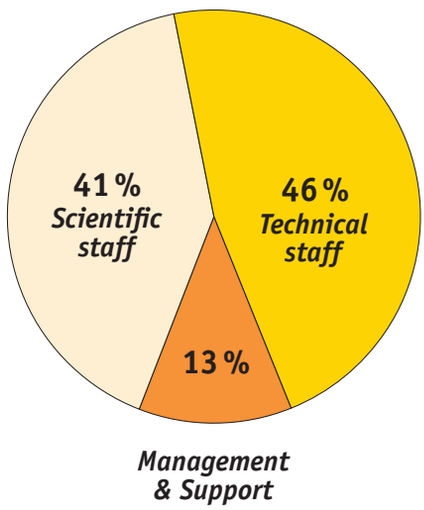
HUMAN RESOURCES

This section distinguishes the IHCP staff into statutory and collaborative staff (trainees, PhD and Post Doc grant holders, visiting scientists, national experts):

Statutory staff distribution – 2002

The DG JRC employs a total of **1,642** officials and temporary agents. Including auxiliary agents the total staff number was **1,939**. In addition to its core staff, the JRC also hosted a total of **294** grant holders, visiting scientists, seconded national experts and trainees coming from the Member States, Candidate Countries or elsewhere (Figures December 2002). Out of the total JRC staff, IHCP employs **186** statutory staff (including officials, temporary agents, and auxiliary agents), and without auxiliary agents a total of **158** staff members:

IHCP Statutory staff
(without auxiliary agents) – 2002



IHCP Statutory Staff (December 2002)	M	F	Total
Officials	53	21	74
Temporary Agents on 5-year renewable contracts	45	36	81
Temporary Agents on 3-year non-renewable contracts	2	1	3
Total IHCP (without auxiliary agents)	**100**	**58**	**158**
Auxiliary Agents on 1-year non-renewable contracts	11	17	28
Total IHCP (with 30 auxiliary agents)	**111**	**75**	**186**

Out of the total IHCP statutory staff (without auxiliary agents) 41% is scientific staff, 46% is technical staff, and 13% provides management and support. The IHCP scientific staff counts on significant expertise in a wide range of disciplines, such as Analytical Chemistry, Biology, Biometrics, Biophysics, Engineering, Food chemistry, Information technology, Science, Medicine, Pharmacology, Physics, Radiochemistry and Toxicology.

Collaborative Staff with Member States and Third Countries

The IHCP hosts a large number of collaborative staff (trainees, grant-holders, visiting scientists, seconded national experts) in order to adjust to its research activities. More specifically, the IHCP hosted 106 collaborative staff in 2002:

IHCP Collaborative Staff (December 2002)	M	F	Total
Trainees	17	17	34
Post-Graduate grant-holders	8	26	34
Post-Doc grant-holders	9	13	22
Visiting scientists	5	5	10
Seconded National experts	5	1	6
Total	**44**	**62**	**106**

BUDGET

The EU Framework Programmes (FP) for Research and Development set out the general research priorities of the European Union in accordance with Article 169 of the EU Treaty. A total budget of € 14,940 million was allocated to the Fifth Framework Programme – FP5 (1998-2002). The JRC (seven Institutes) received an amount of € 1,020 million (7%) out of the total FP5 budget. The IHCP has been attributed an amount of around € 135 million for the period of 1999-2002 (around € 33 million annually).

In general, IHCP credits come from the institutional budget (made available directly from the aforementioned European budget to the JRC); competitive activities; and associated states.

Institutional activities

The JRC defines its broad research areas into its multiannual JRC Work Programme (1999-2002). The JRC Work Programme is updated annually (annual Work Programmes), and where appropriate, adaptations are made following exchanges with "customer" Directorate Generals to review progress and consider new needs. The 2002 JRC Work Programme is arranged according to the following programme lines: a) safety of food and chemicals, b) environment, c) dependability of Information Systems and Services, and d) nuclear safety and safeguards.

The majority of the IHCP projects contribute to the 'Safety of food and chemicals' programme line. The available credits to IHCP are divided into staff expenses, means of execution (maintenance of buildings and equipment, electricity, insurance, consumables, etc.) and operational credits (scientific acquisitions). The following table presents the IHCP institutional budget based on its projects in 2002:

IHCP Institutional Budget 2002–Institutional Projects (K€)

	INSTITUTIONAL PROJECT	Staff expenses	Means of execution	Operational Appropriations	Total
	Safety of food and Chemicals, and health related issues				
FPU	Control of Quality & Safety of Food & Related Items	2,616	90	660	**3,366**
FPU/ GMO	Support to the Implementation of Community Policy on biotechnology (GMO)	3,240	130	660	**4,030**
ECVAM	Validation of alternative methods (ECVAM)	4,810	110	1,700	**6,620**
ECB	Chemical products, environment risk assessment (ECB)	6,319	80	865	**7,264**
BMS	Reliability of Biomedical Devices (REMED)	4,739	50	300	**5,089**
BMS	Minimally Invasive Medical Systems (MIMES)	2,071	20	100	**2,191**
	Environmental-Enhancing Sustainability				
PCE	UV-Radiation, Noice, Indoor Exposure, Electromagnetic Fields (UNIE)	5.067	110	250	**5,427**
	Dependability of Information Systems and services				
SPR	Telematic system for the EU pharmaceutical regulatory activity (ETOMEP)	1.752	35	260	**2,047**
Total		**30,614**	**625**	**4,795**	**36,034**

Competitive activities

The advantages of participating in competitive activities are that IHCP gains access to new expertise, and shares its own competencies and facilities. Competitive activities also provide another source of income besides the institutional budget. In accordance with JRC's own regulations, competitive projects must complement the JRC's mission and must respect the subsidiarity principle.

There are three types of competitive activities:

- Participation in shared-cost activities (SCA) with other successful consortia.
- Activities financed in the context of other EU policies (non-research) upon request of other Commission services (OCA).
- Work undertaken for third parties on a contractual basis (TPW).

Income from Competitive Activities (K€)		
Type	**K€**	**%**
Shared Cost Actions (SCA)	1,090	45
Other Competitive Activities (OCA)	1,027	42
Third Party Work (TPW)	307	13
Total	**2,424**	**100**

In 2002, the IHCP had 21 ongoing Shared Cost Actions. Most of the projects fall under the "Competitive and Sustainable Growth" programme while the remainder fall under the "Quality of Life" Programme. Moreover, the IHCP had one 'other competitive activity' (OCA) on network services for the pharmaceutical regulatory sector.

IHCP Organisational Chart

Director
K. Van Leeuwen

Management Support
B. De Bernardi

Biotechnology and GMOs[1]
G. Van den Eede

European Centre for the Validation of Alternative Methods[2]
T. Hartung

European Chemicals Bureau
G. Vollmer

Physical and Chemical Exposure[3]
D. Kotzias

Biomedical Materials and Systems
H. Stamm

Support to Pharmaceutical Research[4]
F. Argentesi

1. The B&GMO unit was part of the FPU until June 2002. The FPU was transferred from the IHCP (Ispra) to IRMM (Geel, Belgium) during the summer of 2002. B&GMO was officially established in November 2002. G. van den Eede was appointed as Head of Unit on 1st April 2003.
2. M. Balls served as unit head of ECVAM until June 2002. Following his retirement on 1st July 2002, T. Hartung was appointed as Head of Unit on 1st October 2002.
3. The PCE unit was created in June 2002 after the transfer of some selected activities from the Institute for Environment and Sustainability (IES) to the IHCP.
4. F. Argentesi retired on 31st July 2002. The SPR unit ceased to exist at the end of 2002.

Biotechnology and GMOs

Web information resources
http://biotech.jrc.it/
http://engl.jrc.it
http://gmoinfo.jrc.it

Institutional Project
Support to the Implementation
of the Community Policy on biotechnology and GMOs

Some Shared Cost Actions
QPCRGMOFOOD, ENTRANSFOOD

Biotechnology and GMOs (B&GMOs)

In recent years many genetically modified organisms or products derived thereof have been marketed worldwide, mostly for food or feed applications. The EU has adopted a number of regulatory acts to safeguard the human and animal health, to protect the environment and to provide freedom of choice for consumers.

IHCP work in this area is focussed on the development and validation of appropriate methods for detection, identification and quantification of Genetically Modified Organisms (GMOs) in different types of matrices. The European Network of GMO Laboratories (ENGL) that it runs with national control laboratories is seen worldwide as a network of scientific reference. In addition, the Unit has expertise in environmental risk assessment, in bioinformatics and in issues related to sampling. The Unit works closely with the JRC's Institute for Reference Materials and Measurements (IRMM), responsible for the production of GMO reference materials and with the JRC's Institute for Prospective Technology Studies (IPTS) on the elaboration of topical studies.

The Biotechnology & GMOs Unit is the JRC reference for the provision of scientific and technical support to the EC biotechnology regulatory framework and to develop biotechnology expertise in areas relevant for health and consumer protection. It is the youngest of all JRC Units, created on November 1st 2002 as an offspring of the Food Products Unit. The flagship of its activities is the European Network of GMO Laboratories (ENGL) that has been inaugurated in December 2002 as a result of a collaboration between more than 40 control laboratories under the chairmanship of IHCP. Alongside these activities, and in support to ENGL, a number of activities deal with (bio)informatics, with molecular biology research, with method development and validation, and with data mining and sampling. A great deal of attention has also been spent on the development of training courses in collaboration with WHO.

The Unit mostly, but not exclusively, collaborates with DG SANCO and DG ENV. Intensive programmes have also been set up with enlargement countries. In addition, excellent contacts have been established with international research organisations as well as with the biotechnology industry.

THE EUROPEAN NETWORK OF GMO LABORATORIES (ENGL)

The European Network of GMO Laboratories (ENGL) is set up to contribute more effectively to the European harmonisation and standardisation of means and methods for sampling, detection, identification and quantification of GMOs or derived products in a wide variety of matrices, covering seed, grains, food, feed and environmental samples. As such, it is aimed to act as a scientific and technical European Union network of excellence within the context of EU GMO regulation. Projects of excellence and innovation and rapid exchange of data within its members are key issues of ENGL.

Putting in place ENGL is done with the intention to establish a European system for scientific reference for the purpose of:

- Enhancing pan-European harmonisation and standardisation of GMO sampling and analysis.
- Aiding the effective application of such procedures through encouraging the preparation of reference materials and the participation in proficiency testing schemes.

The scope is to create a unique platform for experts where technical items can be put forward and discussed, namely:

- Method development for qualitative and quantitative analysis.
- Molecular biology technology transfer.
- Validation and proficiency studies of methods suitable either for screening of various matrices for the presence of GMOs, or for the estimation of the GMO quantities present.
- Reference material (the responsibility for this work package lies with the JRC's Institute for Reference Materials and Measurements).
- Sampling strategies and procedures for different GM-commodities (seeds, grains, raw material, products for final consumer or mass caterers).
- Databases and bioinformatics and requirements for unique identification of GMOs and setting up of databases that contain these molecular data.

A restricted Web site, the "Bulletin Board of the European Network of GMO Laboratories", has been set up with the purpose to facilitate exchange of information, post notices and view information on news and events.

The network currently consists of 44 EU enforcement laboratories, plus Norway and a number of observers such as representatives from Accession Countries.

The chairmanship is under the responsibility of the Biotechnology and GMOs Unit.

Although four plenary sessions and a number of working group sessions had already been held, the network was officially inaugurated in Brussels on December 4th 2002 in the presence of Commissioner Busquin, JRC Director General, Barry Mc Sweeney and IHCP Director Kees Van Leeuwen.

The event received impressive press coverage: over 35 publications have been issued worldwide in prestigious newspapers and journals such as *Nature, Science* and *The Lancet*.

On the same day, stakeholders' meeting was organised to which about 200 participants took part. The meeting was chaired by Prof. W. Moens (Institute for Hygiene and Epidemiology, Belgium) and the following items have been covered:

- Overview of GM-legislation, with a particular emphasis on the needs for technical and analytical support
  Heidi Hoffmann, Ministry of Federal and European Affairs of North Rhine-Westphalia (Germany).
- Sampling large lots for GMO contamination: what can be reasonably achieved?
  Claudia Paoletti, DG Joint Research Centre - IHCP, Ispra (Italy).
- Detection, identifications and quantification of GMOs and derived products: present and future challenges.
  Arne Holst Jensen, National Veterinary Institute Oslo (Norway).
- Method validation: what can be realistically achieved?
  Hermann Broll, Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin (BgVV) Berlin (Germany).
- Value and applicability of a validated method for control purposes.
  Roger Wood, Food Standards Agency London (UK)
- Past and future of reference materials.
  Heinz Schimmel, DG Joint Research Centre - IRMM, Geel (Belgium).
- The role of the European Network of GMO Laboratories
  Guy Van den Eede, DG Joint Research Centre - IHCP, Ispra (Italy).

BIOINFORMATICS AND DATABASES

Efforts on building a bioinformatics expertise have been mainly focussed on pursuing the development of an ENGL Molecular Register and on the follow-up actions of a brainstorming meeting on a Reference Allergen Register.

ENGL Molecular Register

The ENGL Molecular Register, with the ENGL and the B&GMOs Unit as its primary customers, mainly provides access to a GMO events database and to relevant analysis tools. One of the strengths of the development team lies within the diversity of the profiles: the register has been compiled with input from competent authorities, from bioinformatics experts and from computer scientists.

The development of the Molecular Register has been completed; it has been installed in the unit and it is currently being tested intensively.

Reference Allergen Register

One of the conclusions of an Allergen Database Brainstorming meeting held in 2001 was the need to identify the current state of the art of publicly available allergens database and associated bioinformatics tools. Therefore a review, involving several international partners, has been conducted that has led to two articles proposed for publication.

In addition and to complement the activity on the register itself, the Unit has decided to embark in the INFORMALL concerted action project aimed at developing communication strategies in the food allergy area, to promote the provision of visible, credible sources of information appropriate to different stakeholders including consumers, industry and regulators. The project kick-off is planned for 2003 and should last 3 years.

DATABASES AND INFORMATION TO COMPETENT AUTHORITIES AND TO THE GENERAL PUBLIC

Both the environmental legislation and the GMO food/feed legislation have evolved significantly in 2002. October 17th was a particularly important date because from then on the new Directive (2001/018/EC) came into force. There are a large number of provisions dealing with exchange of communications between authorities, the European Commission and the public.

DG Environment and Member States' Competent Authorities (CA) have mandated the JRC since many years to provide electronic means for the exchange of information on the GMO Notifications Summary, including confidential data, if compliant with confidentiality rules.

Web technology enables all users (Applicants, Member States' Competent Authorities, and European Commission) to retrieve the appropriate amount of information by granting the appropriate level of access and security to each user. Therefore, the Unit has developed a web-based system to facilitate the circulation of information between the Competent Authorities and the European Commission.

The system has two different functions: to grant competent authorities access to an Intranet-based Web interface to enter data on field trials in a user-friendly manner and secondly, once completed, to provide the general public access to an open Internet-site **http: //gmoinfo.jrc.it**. On December 18th the Biotechnology&GMO Unit has trained all competent authorities on how to use the new system.

VALIDATION STUDIES, DATA MINING, SAMPLING STRATEGIES AND TECHNOLOGY TRANSFER

There are a number of EU regulatory acts that lay down the requirement for analytical control for compliance with labelling regulation. For instance, during 2002 Member States were recommended to carry out inspections and controls (2002/66/EC) including taking samples and analysing such samples in laboratories with the aim of monitoring compliance with such Community rules on labelling. Therefore, much of the validation work of the B&GMOs Unit should be looked at in this context, as well as in the light of the operation of the European Network GMO laboratories.

Database on validated methods

The enforcement laboratories must evaluate the method performance in order to select the most appropriate method and, subsequently, must apply the analytical methods that suits best for a certain purpose. To allow this, a database containing a range of information on validated methods for GMO analysis has been compiled.

The direct and user-friendly access is available on-line (**http://biotech.jrc.it/**), and the database currently contains information about 220 validated methods from all over the world. The data reported in this database have been published in peer review journals or in reports from collaborative studies that are available in the public domain. There is general information on the GMO and its application possibilities, information about the method performance as well as essential technical information about the method (i.e., primer sequences, amplicon length, apparatus, control primer sequences, use of certified reference materials, method of amplicon verification etc).

DG SANCO has requested the IHCP whether the information on methods for detection and identification of GMOs reported by CODEX Alimentarius member countries could be hosted on the above database. This work is currently going on.

Validation Studies & Data Mining

During 2002 the majority of the validation studies were carried out within the shared cost action project QPCRGMOFOOD (see below). In addition, the first validation processes for regulatory compliance (in support to the implementation of Regulation 258/97 on novel foods) in collaboration with large industrial companies were initiated. The validation process is a true team effort in which constant performance is required from the method development and co-ordination of the study through the ring trial participation up to the data analysis and evaluation. During 2002, we have up-graded all our procedures related to the validation in order to carry out the ring trials according to the highest international standards, and to collaborate intensively with the ENGL. About 100 laboratories from the Pan-European area expressed their interest to participate in these ring-trials.

Sampling Strategies

The schemes adopted for the sampling of food products lots are of crucial importance to ensure accuracy and precision of GM testing surveys. One of the priorities of the B&GMOs Unit is to identify and develop appropriate sampling strategies to support EU legislation for the detection and quantification of GMOs in different market products.

According to current routine sampling procedures for kernel lots analysis, GM material is assumed to be randomly distributed, so that the producer and consumer's risk can easily be estimated according to the binomial distribution. However, the assumption of random distribution of GM material in kernel lots is likely to be wrong. Indeed, it must be taken into account that industrial activities are well framed in time and space. This generates correlations that, ultimately, will promote segregation during transportation and handling of the material. Our objective is to assess the effect of heterogeneity on the detection of low levels of kernel traits, such as GM material, in large grain or seed lots. The activity of the B&GMOs Unit in this field encompasses three different aspects:

1. Theoretical-statistical work
- Research and development of sampling methods for the detection and quantification of GM materials in different market products.
- Technical evaluation of the available or newly developed sampling plans for GMO detection / quantification with particularly respect to their statistical assumptions and implications.

  The Unit has developed and published a new approach to investigate the effects of different levels of heterogeneity on the accuracy and suitability of different sampling plans for the detection of GM particles within kernel lots. The flexibility of the proposed model allows the simulation of a large number of kernel lots, with defined population characteristics, without imposing any constraint on the distribution of GM kernels. The results of the Unit show that current procedures for the procurement of kernel samples, as stipulated in international guidelines, are sensitive to non-uniform distribution of impurities. In cases of heterogeneous GM material distribution, the samples have a high probability of not correctly representing the lot and/or even not containing any kernels with the trait under investigation (false-negative results). The tools developed by the Unit to evaluate sampling schemes for the detection of GM material in large kernel lots may also be applied to purity testing for other types of kernel traits. These results issue a clear warning with respect to the unconditional acceptance of standardized sampling procedures in absence of the knowledge of GM material distribution in kernel lots.

2. Development of new software (Kernel Sampling Technique Evaluation – KeSTE) to assess the suitability of different sampling protocols as function of lots properties. First, the program allows creating populations. Second, the population developed can be sampled using either a random or a systematic sampling scheme. The user can specify a range of increments (samples) and a range of sample sizes (kernels no. per sample). Response surfaces are built to identify proper sampling techniques.

3. Co-ordination of the EU pan-project **KeLDA** (Kernel Lot Distribution Assessment). This collaboration between ENGL, IRMM and the B&GMOs Unit represents the first study ever carried out to assess the real distribution of GM materials in grain lots imported within EU Member States. The JRC is participating with the B&GMOs Unit and the IRMM in Geel. The project started in May 2002 and is successfully continuing.
   Molecular methods proposed to the participants for the analysis of the KeLDA samples were revised and tested in the molecular biology laboratory of the unit to assess their performances in terms of sensitivity and specificity. The methods are the same the laboratories involved in the project have to use to analyse the increments sampled. Methods include PCR detection of soybean housekeeping gene (lectin) and screening for p35S promoter in soybean. Reference materials were used at GM levels of 2%, 1%, 0.5%, 0.1% and 0%. In addition to the DNA-based detection methods, a protein-based approach for the detection of RoundupReady (RUR) soybean has been included. The method makes use of the Lateral Flow Test Strips (SDI Inc.), an easy to perform and quick approach for the determination of the presence of RUR soybean in test samples. It could be demonstrated that, when proper conditions are applied (proper particle size, dilution of the test sample, incubation time), the LOD (Limit of Detection) of the system is at least 0.033%, which means that the test is capable to detect the presence of 1 particle in 3000. No false positives were detected at the tested conditions. The activity was carried out in collaboration and in support of IRMM, where the strip tests on samples are performed using the protocol developed.

MOLECULAR BIOLOGY LABORATORY

Method, development and optimisation

The principal aim and objective of the Molecular Biology Laboratory of the Biotechnology & GMOs Unit is to perform high quality research for the identification, optimisation and validation of suitable and efficient DNA-based and protein-based analytical methods for the detection and quantification of genetically modified organisms – in raw materials, ingredients and final products – in support to current EU legislation.

Another objective relates to ensuring that the laboratory is at the leading edge of GMO detection technology by exploring and exploiting suitable promising opportunities, to anticipate analytical needs and to be prepared to propose solutions and methodological alternatives.

In this context, the projects and activities carried out in the method optimisation and method development laboratory during the reported period are briefly summarised and described hereafter.

Development and optimisation of multiplex real-time polymerase chain reaction (PCR) based system for the quantification of the CaMV 35S promoter in maize lines.

The aim of the project is to have one unique and therefore convenient quantitative screening system to assess the GMO content in all GMO maize lines currently placed on the market in Europe. After optimisation in terms of primers and probes concentration, DNA extraction and DNA concentration, a full characterisation of the method has been carried out, and performance criteria have been evaluated in an in-house validation.

The real-time PCR method developed and optimised for MON810 for a reliable estimation of the GM content has been applied for the study of the effect of gene copy number in different GM events on the accuracy of GM quantification.

For such a study, amplification reactions have been carried out on the following DNA of GM maize lines approved in Europe: MON810 (DNA extracted from leaf material), Bt-176 (DNA extracted from leaf material and DNA extracted from Certified Reference Material), Bt-11 and T25 (DNA extracted from leaf material). As an outcome of the project, the real-time quantitative method can be applied for accurate quantification of MON810, Bt-11 and Bt-176 CRM materials. For commercial varieties, due the uncertainty on their genetic composition, the method can be reliably applied provided that the genetic composition is known which is subject of the study described below.

Study of the copy number of the maize reference genes zein, invertase, hmg and adh in 30 different GMO and wt maize lines.

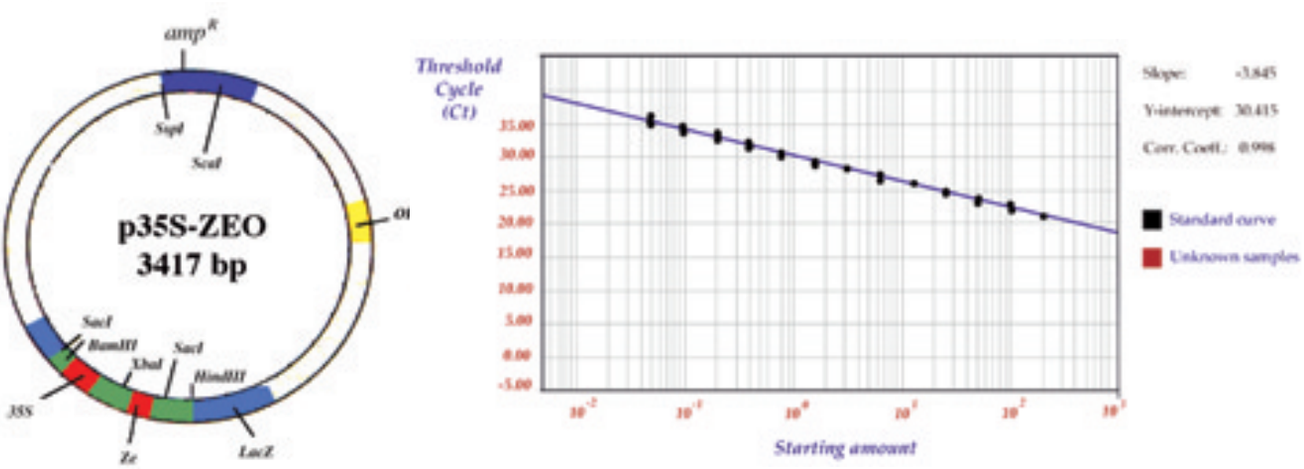
The relative poor characterisation of the variability of the copy number of the most employed maize reference genes causes several problems in the precise quantification of GMOs. In fact, it is possible that different hybrids of the same GMO at the same relative concentration give different quantifications as a consequence of the different copy number of the used reference gene. The study uses a plasmid containing real-time PCR targets specific for the four reference genes at the 1:1:1:1 ratio and several maize lines belonging to almost all breeding groups currently used world-wide.

Development and optimisation of multiplexed real-time PCR quantification systems using novel probe systems (MGB – minor groove binding) recently placed on the market.

The aim of this project is to assess and compare the efficiency of the novel probe design (MGB) with respect to the traditional Taqman degradation probes. A multiplexed method for the quantification of the RoundupReady soybean has been chosen as a model and its optimisation is underway.

Development of novel plasmid based reference materials for the quantification of GMOs.

Plasmids are convenient substitutes of the currently used Certified Reference Materials (CRMs) produced by the IRMM. Two different approaches are under investigation: the first approach uses co-clones of the GMO specific sequences and the reference gene in one single plasmid to plot a serial dilution based standard curve with a high dynamic range. The fixed 1:1 ratio ensures the precision of the quantification. The second approach is based on blending two plasmids at given concentrations producing materials similar to the IRMM CRMs.



Serial dilution based standard curve with a high dynamic range.

Proficiency Testing (PT)

Proficiency Testing (PT) is a quality tool that measures the outputs of a laboratory. PT is complementary to other quality tools that are concerned with inputs such as use of CRMs, implementation of a formal quality system, etc.

The aim of the PT activity of the Biotechnology and GMOs Unit is to establish an internal quality tool, which monitors, over time, the analytical performance of the laboratory in GMO testing.

The PT schemes to which the laboratory has participated in the period covered by this report are:

- **Fapas – GeMMa** (Central Science Lab. – York) Food Analysis Performance Assessment Scheme - 6 Rounds
- **Progetto Trieste** (Tecna Trieste) – 2 Rounds
- **IFR** (Institute of Food Research – Norwich UK) – 1 Round
- **USDA** – GIPSA (Grain Inspection Packers and Stockyards Administration) – 3 Rounds

The table below summarises the types of samples that have been analysed during PT activity.

Raw materials	Processed materials
Soya flour	Baked soybean cake
Maize flour	Baked maize cake
Mixed flour	Toasted soybean flour
Wheat flour	Soya Lecithin
Tobacco dried leaf	Vegetable puree
	Soya milk powder
	Snack food crumb
	Baked biscuit crumbs
	Canned meat

Over 700 analyses have been carried out for GMO screening and identification as well as quantification. A broad range of analytical techniques has been employed including PCR, nested PCR, semi-nested PCR, Real-Time PCR and immunoassay tests (ELISA).

In the period covered by this report, qualitative and quantitative analyses requested by Schemes GeMMA and GIPSA have been carried out. In particular, a protocol for the detection of maize CBH351 (Starlink) and Roundup Ready corn GA21 has been employed with positive results in addition to the routinely event-specific tests used (for the identification of RoundupReady soybean, maize Bt-176, Bt-11, MON810, T25).

Collaboration with IRMM for the certification of CRMs

The replacement material of Bt-176 maize was shipped to the IHCP by IRMM for pre-marketing testing on homogeneity and precision of percentage GM levels. Samples were extracted and tested on Real-Time PCR using a 35S-based quantitative method validated internally. Results showed accuracy of quantification and were provided to IRMM as support to the certification process of the new series of Bt-176 CRM.

Genomics Project

One of the environmental concerns of transgenic crops is about the stability of the transgene constructs. Little is known about what happens with a transgene construct once it is introduced into the plant genome. New varieties are carried over during several plant crosses and undergo different environmental conditions and stresses. On the other hand, detection methods for GM constructs in plants or involving plant specific sequences (the integration site of the insert) need to remain effective and reliable regardless the treatment of the plant, its growth in space or over time. Therefore, it is important to understand how stable the inserts are over time and under several physiological and ecological conditions.

A project addressing the issue of stability was started in collaboration with the CLO in Gent, Belgium, and plant material was provided by the VIB/RUG, Gent.

A part of the project consists of characterising the transgene construct in some transgene crops. Another part concerns a study of stability of the transgene in the model plant Arabidopsis thaliana. This plant has several advantages such as easy growth, quick growing cycle, small genome, a variety of tools applicable and a fully sequenced genome and hence it is successfully used in plant science. Currently, a collection of Arabidopsis thaliana T-DNA insertion lines is being analysed for location of the insert in the genome and studied for stability (re-arrangements, deletions, insertions, single nucleotide polymorphisms) of the flanking regions of the transgene construct. A similar analysis will be carried out for the wild-type line. Comparisons can be made between the pre-insertion site and the inserted site of the genome. The methods that are used in the B&GMOs Unit include anchor PCR, fragment sizing, single strand conformation polymorphism (SSCP) and DNA sequence analysis. As the screening of several thousands of plants is foreseen, a high-throughput system is currently being tested using either radioactive labelling combined with gel-electrophoresis or fluorescent labelling with capillary gel-electrophoresis.

Proteomics in Biotechnology and GMO

The aim of this project is to promote and develop a suitable approach to implement protein based analytical methods for the detection of GMO specific proteins and allergenic proteins in raw materials, ingredients and final products and to carry out validation studies of protein-based methods in support to EU legislation. In 2002 a new infrastructure has been set up enabling the performance of these tasks.

The majority of protein detection methods, currently in use, are based on specific antigen-antibodies immunoreactions therefore the research activity is focused on:

- Development of suitable antibodies against protein allergen.
- Retrieval of commercial GMO antibodies.
- Characterisation of target protein with conventional techniques such as ELISA, mono and two-dimensional gel electrophoresis, Western blots.
- Application of Luminex technology as innovative approach in GMO and allergenic protein detection.

Training & Capacity Building; relation with the Enlargement Projects

In 2002 two training courses on "The Analysis of Food Samples for the Presence of Genetically Modified Organisms" have been organised in collaboration with the Food Safety Programme within the European Centre for Environment and Health - Rome Division (ECR) of the World Health Organisation. The training courses are part of the collaborations between the two Institutions to promote food safety related issues in the WHO European Region, inside and beyond the actual EU borders, taking into special consideration EU Accession Countries, as well as Central and Eastern Countries with economies in transition.

The scope of the training courses is to assist the staff of control laboratories to become accustomed with molecular detection techniques, and to help them to adapt their facilities and work programmes to include analyses to comply with world-wide regulatory acts in the field of biotechnology.

The areas covered during the training courses are:
- DNA extraction from raw and processed materials.
- Screening of foodstuffs for the presence of GMOs by simple and nested PCR.
- Quantification of GMOs in ingredients by real-time PCR.
- Quantification of GMOs in ingredients by ELISA.

Trainees came this time from Brazil, Croatia, Cuba, Cyprus, Czech Republic, Estonia, Germany, Greece, Hong Kong, Hungary, Italy, Lithuania, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, The Netherlands, United Kingdom, United States and Yugoslavia. In addition, The Agricultural Centre from Gödölö delegated one collaborator to both training sessions to learn how to train. A collaboration was initiated for a specific training programme destined to enlargement countries.

Besides the training courses, the Biotechnology & GMOs Unit has offered individual training for specific needs. Training in this topic has been frequently requested due to its importance according to the increasing need to comply with current European legislative framework.

Being aware of the need for a permanent source of information the Biotechnology and GMOs Unit staff has compiled, improved, and edited a Manual, which describes some of the techniques used in its laboratory.

PARTICIPATION IN COLLABORATIVE PROJECTS

QPCRGMOFOOD

The role of the JRC in this shared cost action project, which is is now approaching its end, to co-ordinate work package 5, which deals with the validation of all methods developed in the other work packages. Methods deal with extraction, event-specific detection and event-specific quantitation.

The primary objectives are:
- Develop reliable and transformation-event-specific tests for qualitative and quantitative detection of genetic modifications in food.
- Develop reliable and transformation-event-specific multiplex tests for determination of the diversity of genetic modifications in food.
- Investigate how improved methods for detection of genetically modified foods will influence consumer confidence in food security and trust in science and risk regulators.

The B&GMOs Unit is responsible for the designs of the ring-trials, the co-ordination and organisation of the studies, the analysis of the data, the evaluation and communication of the results and the supply of recom-

mendations for the method application. A general scheme for the validation studies was developed, and on the second half of 2002, reference gene systems for maize, soybean and oilseed rape as well as DNA extraction methods for different maize and soy matrices were tested in multi-laboratory validations. In addition, the pre-validation of nine quantitative GMO-specific methods was launched. The validated methods will be submitted to CEN to become European standards in the GMO testing field.

The molecular biology laboratory activity on preparation and management of validation studies can be summarised as follows:

- Stock samples receipt from method developer.
- Recording and storage of samples and materials.
- Samples check and determination of precise DNA concentrations.
- Preparation of standards and unknowns at the GM levels required.
- Real-time amplification and reagents check before shipping.
- Finalisation of operative protocols.

ENTRANSFOOD

The aim of ENTRANSFOOD is to identify proper research strategies and tools to address issues related to safety and management of transgenic food products. Participants discuss new approaches and establish a permanent platform for communication between the various parties involved. As a result various Working Groups write a number of research papers and position documents.

The main objectives are:

- To identify key issues of the safety evaluation of genetically modified food crops, and to examine whether current research methods are adequate to characterise specific safety hazards.
- To design new (in-vitro) test methodologies for safety and nutritional evaluation of whole complex foods, which are of sufficient sensitivity and specificity.
- To address the risks of gene transfer from genetically modified organisms to the bowel microflora of humans and animals.
- To examine new strategies for the detection of genetically modified foods, which enable detection at specific threshold levels for raw materials, processed products and food ingredients.
- To develop a communication platform of producers of GMOs, scientists involved in research and safety evaluation of GMOs, retailers, regulatory authorities and consumer groups with the scope to improve safety assessment procedures, risk management strategies and risk communication.

The role of the Biotechnology and GMOs Unit is to chair Working Group 3 on “gene transfer in relation to the safety of food and feed derived from GM-plants”. The Biotechnology and GMOs Unit will also involved in the organisation of the closing meeting, due to take place in Rome on 29 to 30 May 2003.

SELECTED PUBLICATIONS 2002

ANKLAM, E.; GADANI, F.; HEINZE, P.; PIJNENBURGH, H.; VAN DEN EEDE, G. – *Analytical Methods for Detection and Determination of Genetically Modified Organisms in Agricultural Crops and Plant-Derived Food Products. European Food Research & Technology,* Vol. 214, (2002) 3-26

ANKLAM, E.; HEINZE, P.; KAY, S.; VAN DEN EEDE, G.L.M.; POPPING, B. - *Validation Studies and Proficiency Testing. Journal of AOAC International,* Vol. 85, No. 3 (2002) 809-815

BONFINI, L.; HEINZE, P.; KAY, S.; VAN DEN EEDE, G. – *Review of GMO Detection and Quantification Techniques* – EUR 20384 EN (2002)

BONFINI, L.; KAY, S.; HEINZE, P.; VAN DEN EEDE, G. – *Report on GMO Detection, Identification and Quantification Methods Submitted to Collaborative Studies* – EUR 20383 EN (2002)

KAY, S. – *Report to the 3rd Meeting of the European Network of GMO Laboratories on the Validation Study of an ELISA Kit for the Quantification of Roundup Ready® Soy Fraction Matrices in Animal Feed Ingredients,* April - October 2001 – EUR 20234 EN (2002)

KAY, S.; PAOLETTI, C. – *Sampling Strategies for GMO Detection and/or Quantification* – EUR 20239 EN (2002)

PAOLETTI, C.; DONATELLI, M.; KAY, S.; VAN DEN EEDE, G. – *Simulating Kernel Lot Sampling: the Effect of Heterogeneity on the Detection of GMO Contamination. Seed Science and Technology* – in press

VAN DEN EEDE, G.; KAY, S.; ANKLAM, E.; SCHIMMEL, H. - *Analytical Challenges: Bridging the Gap from Regulation to Enforcement.* Journal of AOAC International, Vol. 85, No. 3 (2002) 757-761

PRIZES / AWARDS TO STAFF FOR THEIR ACHIEVEMENTS

Janna Puumalainen, co-ordinator of the data mining and sampling project received the JRC Young Scientist Award for Environmental Research in December 2002 and in addition, she received an award for the achievements in an international career by the Faculty of Forestry of the University of Joensuu, Finland, on the 11th of October, 2002.

CONTACTS

The Unit has put a lot of effort to implement a dynamic policy of communication and of public relations. Therefore it is suggested to visit regularly each of the three web-sites listed and to have a look, for instance at the Biotechnology and GMOs Newsletter that is regularly published on-line, together with an overview of all on-going and planned activities, papers published, training courses and conferences planned.

Head of Unit
Guy van den Eede
Tel.: +39 0332 789755
Fax: +39 0332 785483
guy.van-den-eede@cec.eu.int

Communications and Public relations
Rossella Speroni
Tel.: +39 0332 785959
Fax: +39 0332 785438
rossella.speroni@cec.eu.int

Web information resources
At IHCP site
http://ihcp.jrc.cec.eu.int/Activities/ACTVali/ACTVali.html
At the ECVAM site
http://ecvam.jrc.it
At the ECVAM Scientific Information Service site
http://ecvam-sis.jrc.it/

ecvam

European Centre for the Validation of Alternative Methods

Institutional Project
The validation of alternative methods

Some Shared Cost Action
Comparison and Validation of Novel Pyrogen Tests based on the Human Fever Reaction

The Validation of Alternative Biomedical Test Methods

The European Centre for the Validation of Alternative Methods (ECVAM) is an international reference centre for the development and acceptance of alternative testing methods to replace, reduce or refine use of laboratory animals in the biomedical sciences with emphasis on toxicological assessments. ECVAM was established by a communication of the European Commission (SEC 91/1794) referring to a requirement in the animal protection Directive 86/809/EEC.

ECVAM's work is focused on the development and evaluation of in vitro methods (e.g. cell and tissue cultures), the use of computer modelling based on structure-activity relationships, and on physiological and biokinetic modelling. ECVAM's role is to co-ordinate international validation studies, to act as a focal point for the exchange of information, to set up and maintain a database on alternative methods, and to promote dialogue among legislators. Moreover, ECVAM plays an active role in the pre-normative research activities of the JRC.

Due to the political sensitivity of its duties, ECVAM, uniquely at the JRC, has its own Scientific Advisory Committee (ESAC) with participation from all Member States, relevant industrial associations, academic toxicology, the animal welfare movement, as well as other Commission services with an interest in the alternatives area.

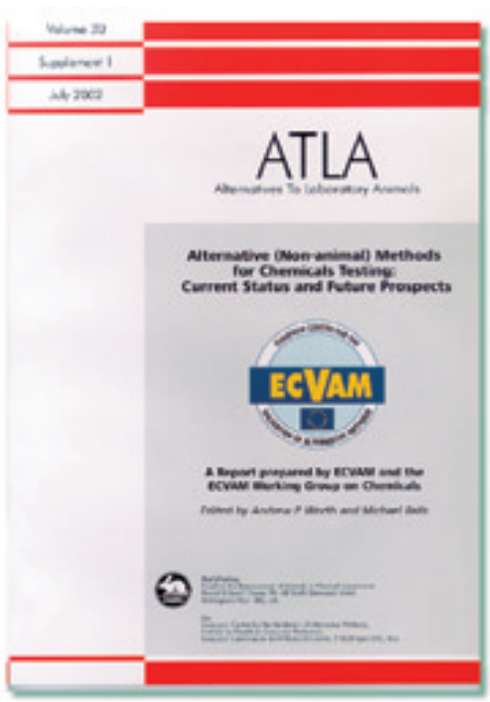
Consequently, ECVAM has established a wide international network of collaborators in the Member States, and all over the world. ECVAM also works in close collaboration with other Commission services, such as DG Environment, DG Enterprise, DG Research and DG Health and Consumer Protection.

ECVAM and the Chemicals Policy

Serious decisions must be taken on the potential effects of various kinds of chemicals and products to guarantee their safe handling and to protect consumers health as the ultimate goal. To this aim, the Commission issued a White Paper outlining its chemicals policy strategy with the overall aim to provide a uniform regulatory framework for chemical substances harmonising testing requirements for existing and new chemicals. The Council and the European Parliament has asked for ECVAM's strong involvement in order to minimise the use of experimental animals for this purpose and to speed up the policy implementation throughout the development and validation of more cost-effective and faster in vitro techniques.

Responding to this request, ECVAM established an ad-hoc Working group on Chemicals with the ultimate goal to propose a strategy on the development and validation of new alternative (non-animal) methods. To best achieve this objective, ECVAM organised several meetings of this working group and its subgroups in 2002, which resulted in the publication of the comprehensive report "Alternative (non-animal) Methods for Chemicals Testing: Current Status and Future Prospects" (Edited by Worth, A. & Balls, M. (2002) ATLA, vol.30, suppl. 1). Following the recommendations of the report ECVAM established several project management groups for all areas of chemical safety testing and initiated a fund of the chemicals industry.

Furthermore, the year 2002 brought news on ECVAM's leadership. Thomas Hartung from the University of Konstanz was appointed as new Head of Unit after the retirement of Micael Balls.



The activities of ECVAM can be subdivided into the following areas: a) laboratory–based tasks, i.e. areas where ECVAM carries out mainly research and development, b) non-laboratory tasks, i.e. areas, where ECVAM organises (pre)validation studies only c) the ECVAM Scientific Information Service (SIS), and d) other activities.

LABORATORY-BASED TASKS

Carcinogenicity and Metal Toxicity

A database on concurrent cytotoxicity and morphological transformation induced by 30 inorganic and/or organometallic compounds in Balb/3T3 mouse fibroblasts was established. This cell transformation assay is now available for prevalidation. Furthermore, the screening of the genotoxicity of 20 metal compounds by the human lymphocyte micronucleus assay coupled with fluorescence in situ hybrydization (FISH) was carried out. In addition, an evaluation of the genetic damage induced by 15 metal species by using the Comet assay and a new developed protocol employing the human lymphoblastoid cell line (TK6) was completed.

In other areas investigations included screening studies with the setting of dose-effect relationships for the determination of basal cytotoxicity of more than 40 metal compounds employing different cell lines, as well as studies on the effects of 25 metal compounds on the immune system. A comparative study was carried out for the embryotoxicity and teratogenicity of mercury dichloride and methyl mercury assayed by the Frog Embryo Teratogenesis Assay-Xenopus (FETAX) and a study on the use of gene expression as a potential molecular biomarker of early effects of metals.

Furthermore, analytical methods were developed for online speciation of chemical forms of arsenic and platinum in culture media and cytosol of cells by HPLC-ICP-MS, for metabolic studies as key factor for the interpretation of the cytotoxic response.

Haematotoxicity and Anti-Cancer Drugs

In vitro haematotoxicology provides the opportunity to study the effects of toxicants directly on the relevant human target tissues, like bone-marrow and cord blood cells, reducing toxicological uncertainties due to animal/human extrapolation.

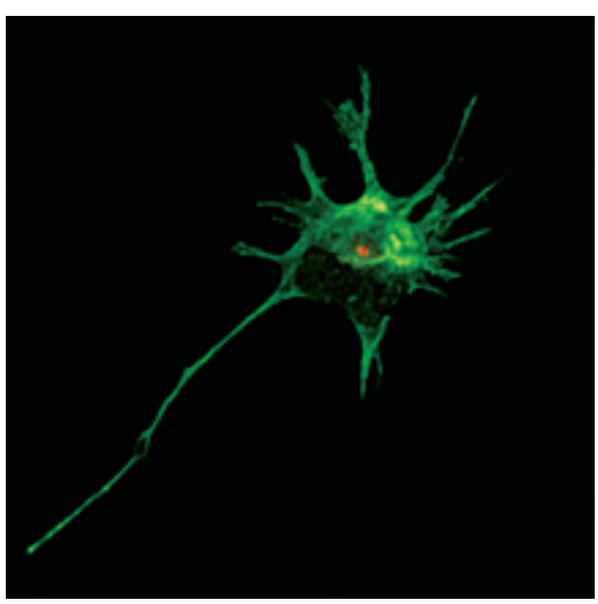
In 2002 a refinement of clonogenic assays for 'high-throughput' methods has been carried out, comparing dose-response curves and IC50s obtained with the traditional assays and microplate-systems.

Genetic damage to hematopoietic cells may occur in the absence of any overt hematological sign. The development of tissue-specific screening systems to detect adverse effects of xenobiotics on target genes is needed for priority settings of chemicals and drug candidates. The toxicity of various compounds to the human cord blood cells has been evaluated by flow cytometry and confocal microscopy, as well as macroarray analysis.

Moreover, the ongoing study of the effects of various p53 mutants on cell growth and apoptosis may help to understand the contributions of environmental, occupational and recreational exposure to the process of carcinogenesis. In this field, the evaluation of the chemical-induced modulation of apoptosis and cell cycle-related proteins in HepG2 and Hep3B cell lines has been carried out.

Metabolism, Neurotoxicity and Immunotoxicity

Metabolism is the process by which an administrated chemical is structurally changed in the body by either enzymatic or non-enzymatic reactions. Information on the metabolism of a substance is of crucial importance in the evaluation of toxicological data. Common genetic polymorphisms leading to absent, low or increased activities in these may influence their toxicological potential, and alterations in metabolism may have serious implications such as inefficient repair of chemical-induced genetic damage. High-throughput in vitro test methods were established using genetically engineered cell lines harbouring polymorphic forms of metabolising enzymes for studies of polymorphism-mediated effects after chemical challenge.



Genetically engineerd PC12 neuronal cell line

On the other hand, some of these enzymes are inducible in response to foreign compounds, which may result in an increase in toxicity caused by increased formation of reactive metabolites. As a follow-up of an ECVAM Workshop and an ECVAM Task Force Report on the applicability of hepatocytes in routine testing, an ECVAM interlaboratory prevalidation study on the response of cultured human hepatocytes to model such inducers was initiated in collaboration with an international consortium.

Up to now, no in vitro methods for evaluating the neurotoxic hazard of a chemical have been validated. The current guidelines from OECD for the Assessment of Neurotoxic Effects of chemicals are based on in vivo studies. Based on expert advice of a task force and collaborators, ECVAM established a strategy for the evaluation of the neurotoxic potential of chemicals using a tiered approach including a battery of mechanistic-based tests, aiming to provide neuropathological, neurophysiological and neurochemical information.
At present, the toxicological significance of immune responses is under discussion. Immunotoxicity comprises any effect on the immune system, which might result in increased susceptibility towards infection or allergy. At ECVAM, a whole blood cytokine release model has been developed to predict the toxicity of foreign compounds towards the immune system in a simple, fast, economical and reliable way.

Furthermore, the pyrogenicity validation project (5th Framework Programme Project "Comparison and validation of Novel Pyrogen Tests based on the Human Fever Reaction") reached an important stage. Four of the six cell-based models passed successfully the validation phase.

Molecular Biology and Toxicogenomics

The availability of whole genome DNA sequences and reagents has led to the development of high throughput methods for monitoring expression level of thousands of genes simultaneously. Toxicogenomics is a new subdiscipline derived from a combination of toxicology and genomics, which allows studying the impact of chemicals and drugs on gene expression. In the past decades several in vitro tests have been developed to measure toxicity. Fundamental to all of these methods is the fact that toxicity is often preceded by and results in alterations of gene expression. In many cases these changes in gene expression are far more sensitive, characteristic and measurable endpoints than the toxicity itself.

Toxicants can therefore be identified and their mechanisms of action determined by simultaneously analyzing the toxicant-induced expression pattern. This can be done by the microarray technology. ECVAM has set up this novel technology, which seems very promising for a second generation of alternatives. The aim is to use it in critical key areas where suitable alternatives are lacking, such as carcinogenicity of non-genotoxic compounds, repetitive dose toxicity or endocrine disruptors.

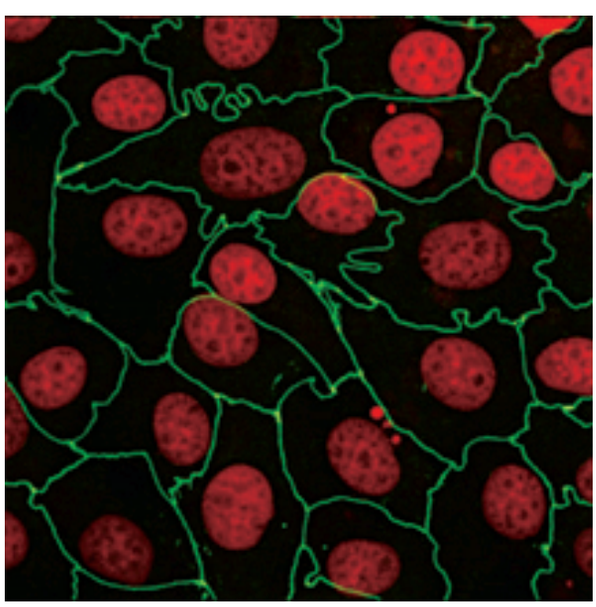
Nephrotoxicity, Barriers and Long-Term Toxicology

In vitro tests are being developed at ECVAM and with collaborators, for detecting toxicity to various biological barriers after short and long-term exposure to potential toxicants. Since barrier function is an important determinant of absorption and distribution, in vitro models are developed to assess the passage of chemicals across biological barriers, such as the renal barrier and the blood-brain barrier.

The prevalidation study of trans-epithelial resistance and inulin permeability as endpoints in in vitro nephrotoxicity testing and the study on the evaluation of the reproducibility and transferability of flow cytometry and confocal microscopic endpoints have been finalised. ECVAM currently supports the development and refinement of a Caco-2 cell in vitro model of intestinal barrier function.

An evaluation of a cell culture medium supplement to replace the use of animal serum was carried out.

In the context of repeated-dose toxicity, perfusion cell culture systems and other systems available are under evaluation.



Immunofluorescent staining for tight junctions (green) and nuclei (red) of intact (control) renal LLC-PK1 cells

Reproductive Toxicology and Cardiotoxicity

In order to reduce the animal consumption for embryotoxicity testing three methods for in vitro testing have been validated during the last years. The results of the definite phase and the evaluation of the prediction model have been published and ECVAM's advisory committee has endorsed the scientific validity of the three methods. An additional workshop on the practical ap-

plication of the methods is planned for 2003 in order to evaluate and promote the application of the three methods. ECVAM has trained scientists from academia and industry on one of the validated test.

In addition, ECVAM has continued the project of using reporter genes for detecting tissue specific effects of chemicals on the developing embryo. This project has been done in close collaboration with the University of Cologne/Germany. The outcome of the project has led to the foundation of a Biotech Company in Cologne. In addition, the reporter gene technology was employed to establish a system that allows detecting the differentiation induction of chemicals within four days.
In order to discuss the potential of human stem cells for in vitro toxicology and therapeutically application a workshop has been held. The participants formed a consortium and submitted an expression of interest to DG RTD on the quality and safety issue of stem cells.

NON-LABORATORY TASKS

Acute and systemic toxicity

In vivo acute systemic toxicity testing is required by regulatory bodies to assess the hazard of chemicals, or any other test material, after single exposure, and is usually the first step in a series of toxicological studies. The classical oral LD50 test for assessing the median lethal dose (LD50, i.e. the dose that kills half the animals in the experimental group) has been deleted from EU legislation. Three alternative methods have been adopted, but they are still based on the use of animals.

In 2002 ECVAM started a joint validation study together with ICCVAM (U.S. Interagency Coordinating Committee on the Validation of Alternative Methods) to evaluate the relevance of data from two standardised basal cytotoxicity methods in predicting rodent oral LD50 and human lethal concentrations. The results from this study will establish to what extent the prediction of oral LD50 values can be used to reduce the number of animals in oral acute toxicity testing.

Biologicals

Biologicals are products such as vaccines, immunosera, immunoglobulins, hormones, monoclonal and polyclonal antibodies, which undergo extensive quality control during their production involving often tests on animals.

In 2002 the ESAC endorsed three statements in the area of biologicals: one on the scientific validity of an ELISA procedure for the batch potency testing of swine erysipela vaccines and two on the deletion of animal tests for the routine safety testing of veterinary vaccines and for the batch potency testing of a hormone. A prevalidation study on the use of PCR for the quality control of avian vaccines was initiated. A workshop on Three Rs approaches for the quality control of rabies vaccines was held and the workshop report will be published in 2003. ECVAM participated in the first part of a validation study of an ELISA procedure for the batch potency testing of Clostridium perfringens vaccines organised by the German competent authority. ECVAM continued to submit comments on revision proposals of European Pharmacopoeia monographs in order to promote the Three Rs concept in the quality control of biologicals.

In the field of biologicals ECVAM mainly collaborates with the competent authorities of the EU Member States, the European Pharmacopoeia, industry, and the Advisory Group on Alternatives to Animal Testing in Immunobiologicals (AGAATI).

Topical Toxicity and Human Studies

Important progress was made in the field of skin and eye irritation where alternative methods are urgently needed in relation to the EU Chemicals Policy and the 7th amendment to the Cosmetics Directive 76/768/EEC. Comments and input on proposals for a 7th amendment to this Directive were provided through interservice consultations.

With regard to skin irritation, the ECVAM Skin Irritation Task Force organised an international validation study on three in vitro methods: the EPIDERM and EPISKIN assays and the Skin Integrity Function Test (SIFT). This validation study, which aims at the replacement of the traditional Draize rabbit skin test, will take place in 2003.

A survey was organised, in collaboration with the European Chemicals Bureau, which involved the National Coordinators for Testing Methods and the Competent Authorities of the EU Member States, to establish the uses of alternative methods for eye irritation formally accepted by regulatory authorities. The survey led to a recommendation to carry out weight-of-evidence reviews on some in vitro methods so that they could be validated and accepted into regulation.

Two collaborative studies on skin irritation testing with non-invasive technology and on phototoxic potency testing were initiated.

THE ECVAM SCIENTIFIC INFORMATION SERVICE (SIS)

In line with its institutional duties ECVAM has established and maintains the Scientific Information Service (SIS) to disseminate factual and evaluated (ready-to-use) information on advanced alternative methods for toxicology assessments. SIS mainly provides full method descriptions, including their development and validation status, the test protocols for their performance , and information on test results.

The year 2002 has seen the further consolidation of ECVAM as an information centre. The SIS reached 1500 active registered users to its online databases. An analysis of statistics and a questionnaire is under development. At the same time, the information contents of SIS is continuously being updated in various fields of in vitro toxicity testing carried out in collaboration with various European Institutes.

Moreover, ECVAM established its web site and made it available on the Internet at the address: **http://ecvam.jrc.it**, which offers, among others, numerous documents for download related to ECVAM's work and is linked to SIS databases.

The 1st version of the ECVAM Thesaurus project, a systematically ordered collection of harmonised terms, is being prepared for its online availability for practical application by the end-user. This project was a result of a collaboration with the Head of the Thesaurus section of the US National Library of Medicine, the world leading authority in the area of thesauruses applied to biomedical sciences.

OTHER ACTIVITIES

ECVAM Workshops & Task Forces

ECVAM workshops are held to review the current status of various types of alternative tests and their potential uses, and to identify the best way forward. Task Forces focus on more tightly defined targets. In 2002 two meetings of ECVAM Task Forces on Skin Irritation and Hormones, were held as well as the Workshop on the Three Rs Approaches in the Quality Control of Rabies Vaccines.

Good Laboratory Practices and Good Cell Culture Practices

In the course of executing its mission to validate in vitro methods as alternatives for conventional animal testing, ECVAM has been the catalyst in considering quality control issues for in vitro studies in general. Based on an ECVAM workshop on 'The principles of good laboratory practices: application to in vitro toxicology studies', OECD initiated the set-up of a task force for considering the issuing of an OECD Guidance document on "Good Laboratory Practices (GLP) and in vitro toxicological studies". The Interagency Coordinating Committee for Validation of Alternative Methods (ICCVAM) in the United States, through its GLP Subcommittee, shares these goals and therefore, both ECVAM and ICCVAM are collaborating strongly on this topic.

The maintenance of high standards is fundamental to all in vitro sciences and therefore, ECVAM continues to promote this spirit by the recent publication of an ECVAM Task Force Report on Good Cell Culture Practices.

MAJOR EVENTS

The ECVAM Status Seminar

A little bit more than ten years after the establishment of ECVAM, the Unit organised a Status Seminar to critically review the contributions of ECVAM to its four main duties and to identify priorities for future activities with regard to these tasks and with emphasis on the EU Chemicals Policy, the 7th Amendment to Directive 76/768/EEC on Cosmetics and Directive 86/609/EEC on animal welfare. Collaborators and stakeholders of ECVAM, in addition to the ECVAM staff and members of the JRC, attended the seminar. The scientific programme consisted of six sessions with 48 platform presentations and a poster session. The unanimous judgement was that ECVAM has achieved the position of an international reference centre in the area of animal alternatives for test development and validation.

Press Conference

A stakeholder and press conference on Research into Alternatives to Animal Experimentation and the Three Rs concept was jointly organised by DG RTD and DG JRC. Parts of the proceedings of that conference were submitted by ECVAM to DG Research.

Awards

Enrico Sabbioni received the 2002 Hevesy Medal Award on 17th June in Antalya, Turkey, in recognition of his outstanding career contribution to radioanalytical chemistry, particularly in biomedical applications over 40-year period. The Hevesy Medal Award is the premier international award of excellence to honour outstanding achievements in radioanalytical and nuclear chemistry.

SELECTED PUBLICATIONS 2002

Alternative (non-animal) methods for chemicals testing: current status and future prospects. A report prepared by ECVAM and the ECVAM Working Group on Chemicals. Edited by WORTH, A.P. & BALLS, M. (2002) ATLA 30, supplement 1

The proceedings of the ECVAM Status Seminar "Alternatives to Animal Experiments: Progress Made and Challenges Ahead", 4-6 June 2002, JRC Ispra, Italy. Edited by BALLS M. (2002). ATLA 30, supplement 2

GRIBALDO L, ALISON M, ANDREWS P., BREMER S., DONOVAN P., KNAAN SHANZER S., MERTELSMANN R., SPIELMANN H., TESTA N., TRIFFITT J., ZIPORI D. & DEWYNTER E. *Meeting summary: European workshop on stem cells,* European Centre for the Validation of Biomedical Testing Methods, Institute for Health and Consumer Protection, Joint Research Centre, Ispra, Italy, November 21-23, 2001. Experimental Hematology 30, 628-633

GENSCHOW E. SPIELMANN H., SCHOLZ G., SEILER A., BROWN N., PIERSMA A., BRADY M., CLEMANN N., HUUSKONEN H., PALLIARD F., BREMER S. & BECKER K. (2002) *The ECVAM International Validation Study on In Vitro Embryotoxicity Tests; Results of the Definite Phase and Evaluation of Prediction Models*. ATLA 30, 151-176.

HALDER, M., HENDRIKSEN, C.F.M., CUSSLER, K. & BALLS, M. (2002). *ECVAM's contribution to the implementation of the Three Rs in the production and quality control of biologicals*. ATLA 30, 93-108

HARTUNG, T., BALLS M., BARDOUILLE C., BLANCK O., COECKE S., GSTRAUNTHALER G., LEWIS D. (2002). *ECVAM Good Cell Culture Practise Task Force Report 1*. ATLA 30, 404-444

PAZOS P., FORTANER S., PRIETO P. (2002). *Long-term in vitro toxicity models: comparison between a flow cell bioreactor and static cell cultures based on membrane technology*. ATLA 30(5): 515-523

MAZZOTTI F., SABBIONI E., PONTI J., GHIANI M., FORTANER S., & ROSSI G. L. (2002). *In vitro setting of dose-response relationships of 32 metal compounds in the Balb/3T3 Cell Line, as a basis for predicting their carcinogenic potential.* ATLA 30, 209-217

ZUANG, V., BALLS, M., BOTHAM, P.A., COQUETTE, A., CORSINI, E., CURREN, R.D., ELLIOTT, G.R., FENTEM, J.H., HEYLINGS, J.R., LIEBSCH, M., MEDINA, J., ROGUET, R., VAN DE SANDT, J.J.M., WIEMANN, C. & WORTH, A.P. (2002) *Follow-up to the ECVAM Prevalidation Study on In Vitro Tests for Acute Skin Irritation. ECVAM Skin Irritation Task Force Report 2*. ATLA 30, 109-129

CONTACTS

Head of Unit
Thomas Hartung
Tel.: +39 0332 786256
Fax: +39 0332 785336
thomas.hartung@cec.eu.int

Acute and Systemic Toxicity
Silvia Casati
Tel.: +39 0332 786445
Fax: +39 0332 785336
silvia.casati@jrc.it

Analytical Chemistry
Salvador Fortaner
Tel.: +39 0332 785079
Fax: +39 0332 785336
salvador.fortaner@jrc.it

Biologicals and PECO
Marlies Halder
Tel.: +39-0332785550
Fax: +39-0332785336
marlies.halder@jrc.it

Carcinogenicity and Metal Toxicity
Enrico Sabbioni
Tel.: +39 0332 789070
Fax: +39 0332 785994
enrico.sabbioni@jrc.it

Haematotoxicity and Anticancer Drugs
Laura Gribaldo
Tel.: +39 0332 789267
Fax: +39 0332 785336
laura.gribaldo@jrc.it

Metabolism and Neurotoxicity, Pyrogenicity and Immunotoxicity testing and GLP
Sandra Coecke
Tel.: +39 0332 789806
Fax: +39 0332 785336
sandra.coecke@jrc.it

Molecular Biology
Raffaella Corvi
Tel.: +39 0332 785266
Fax: +39 0332 785845
raffaella.corvi@jrc.it

Nephrotoxicity, Barriers and Long-Term Toxicology
Pilar Prieto
Tel.: +39 0332 78 5534
Fax: +39 0332 785336
maria.prieto-pilar@jrc.it

Reproductive Toxicology and Cardiotoxicity
Susanne Bremer
Tel.: +39 0332 785914
Fax: +39 0332 785336
susanne.bremer@jrc.it

The ECVAM Scientific Information Service (SIS)
Annett Janusch Roi
Tel: +39 0332 785570
Fax: +39 0332 785845
annett.roi@jrc.it

Topical Toxicity and Human Studies
Valèrie Zuang
Tel.: +39 0332 785843
Fax: +39 0332 785336
valerie.zuang@jrc.it

ecb

European Chemicals Bureau

Web information resources
At IHCP site
http://ihcp.jrc.cec.eu.int/NEW_ACTIVITIES/ACTIndex.html
At the European Chemicals Bureau site
http://ecb.jrc.it/

Institutional Project
Chemical products, environment risk assessment

The ECB provides scientific and technical support to the conception, development, implementation and monitoring of EU policies on dangerous chemicals. The ECB supports the development and harmonisation of testing methods; the legal classification and labelling of substances; the management of risk assessment of substances; the notification of new substances; the authorization of dangerous biocides; and the information exchange on import and export of dangerous substances. Directives supported are 67/548/EEC, 93/67/EEC, 96/56/EC, 97/56/EC, 98/8/EC and the regulations are 2455/92, 793/93, and 484/94.

Main partners of the ECB are the authorities of the EU Member States and Norway, Commission services (such as DG Environment and DG Enterprise), the chemical industry, and NGOs. The ECB manages and chairs around 40 meetings per year with the aforementioned stakeholders.

The New EU Chemicals Policy

The recent White Paper on the Strategy for a future Chemicals Policy (COM (2001) 88 final) presents the Commission proposals for a new EU chemicals policy. The IHCP (the ECB and ECVAM) will play a central role in the establishment of this policy through the:

- Further expansion of activities in this field including the responsibility for approximately 100,000 registrations on 30,000 chemicals.
- Establishment of a central system of **R**egistration, **E**valuation, and **A**uthorisation of **CH**emicals–the so-called REACH-IT system–to host all chemicals data and to support the authorities of the EU Member States.
- Restriction and authorisation procedure on chemicals of high concern.
- New testing strategy using alternative tests.

The following sections will focus on a) the process of the evaluation of (existing and new) substances; b) the authorization of biocides; and c) the information exchange on import/export of dangerous substances.

THE PROCESS OF THE EVALUATION OF SUBSTANCES

There is an arbitrary distinction between 'existing' and 'new' substances in Europe, which affects the evaluation process. Existing substances are defined as those substances that were already on the EU-market, and listed in the European Inventory of Existing Commercial Substances (EINECs) by 18 September 1981 – an inventory containing 100,000 substances. New substances are those placed on the EU market for the first time after 18 September 1981. These new substances must be notified before being placed on the market, after which they are registered in the European List of Notified Chemical Substances (ELINCs).

In contrast to the new substances, existing substances have never been subjected to a systematic testing regime. When the requirement for testing and notification of 'new' substances was introduced in 1981, substances already on the market were exempted. Only in 1993, the Council Regulation 793/93 introduced a framework for the evaluation and control of 'existing' chemical substances, thereby complementing the already existing rules for new substances governed by Council Directive 67/548/EEC.

The ECB supports the three first steps of Council Regulation EEC 793/93: data collection, priority setting, and risk assessment of substances. In consultation with EU Member States the Commission must regularly draw up lists of priority substances, on the basis of collected information, taking into account their potential effects to humans or the environment.

Relevant EC legislation on Substances	
Directive 67/548/EEC	Classification & Labelling, Notifications, Testing Methods
Directive 93/67/EEC	Risk Assessment New Substances
Directive 98/8/EC	Biocides
Regulation (EEC) 793/93	Existing Substances
Regulation (EC) 1488/94	Risk Assessment Existing Substances
Regulation (EEC) 2455/92	Export/Import
Directive 76/769/EEC	Restriction on Marketing and Use
Directive 91/414/EEC	Plant Protection Products

The following sub-sections describe in more detail the stages of the evaluation process of substances.

The harmonization of Testing Methods

Harmonized testing methods must exist in order to evaluate the properties of various substances. The ECB is responsible for the technical and scientific work needed for the development, introduction, and adaptation to technical progress of testing methods of Annex V to Directive 67/548/EEC (and its adaptations). Annex V contains standardized testing methods for the determination of the intrinsic properties of chemical substances, which allow for the characterization of potential hazards for people and the environment. Data provided by testing methods constitute the basis for a proper classification and labelling of chemicals and for risk characterization. Moreover, the use of these standardized methods ensures the mutual acceptance of data, and the free circulation of goods between countries. The ECB activities in this area are coordinated with the OECD and other international organizations.

In 2002, the main achievements in introducing or updating testing methods were the:

- 6 additional new or updated methods were prepared for Annex V, including several new or revised alternative methods (reduction and refinement) and updating of animal tests including new strategies to reduce animal use.
- 7 methods in preparation, including four new or revised in vitro methods.
- An interim strategy allowing the use of some in vitro methods for eye irritation was approved.
- Further development of methods for MMMF: Closure of the first phase of the 90 days inhalation study, a scientific paper summarizing the results in preparation. New method for LWGMD finalized.
- Electronic informal versions of all (85) in force Annex V methods were produced and made available in the ECB web site.
- A guidance document on granulometry of chemical substances was published.

Legal classification and labelling (existing and new substances)

The ECB is in charge of technical and scientific issues for the Adaptation to Technical Progress (ATP) of Annexes I, II, III, IV, VI, and IX to Council Directive 67/548/EEC on the classification, packaging and labelling of dangerous substances. The ECB's work entails the preparation, chairing and follow-up of meetings of the Commission Working Group on Classification and Labelling (composed of experts from EU Member States and observers from the EEA Member States, industry and NGOs); the co-ordination of meetings between EU Member States and industry and the provision of information to other Commission services.

The 29th ATP preparations were initiated during 2002. The ATP will include – besides new testing methods - an updated foreword to Annex I (Note K), together with approximately 220 new or revised Annex I entries for existing substances, 382 entries for new substances and 16 entries for confidential pesticides.

A technical working group, chaired by the ECB, was set up to prepare the implementation of the Globally Harmonised System (GHS) of classification and labelling within the Community in the context of the White Paper on a future chemical policy.

Risk assessment for existing chemicals

All substances (existing and new) on the priority list must undergo an in-depth risk assessment to examine the risks posed to humans and the environment (terrestrial, aquatic and atmospheric eco-systems). The risk assessment follows the framework set out in Regulation 1488/94, and implemented in the detailed Technical Guidance Documents on Risk Assessment for New and Existing Substances.

The first draft of the risk assessment reports are prepared by the Member State which acts as 'rapporteur', and is submitted to the Technical Meetings for discussion. The ECB mediates the technical meetings, which attempt to reach consensus on the conclusions of the risk assessment. After adoption of the risk assessment, three publications on Existing chemicals are produced:

- Comprehensive risk assessment report (2 formats): IUCLID and ECB homepage.
- Summary: ECB homepage.
- Conclusions in the Official Journal or the European Communities.

The following table shows the risk assessment reports of existing substances that were finalised in 2002, and the Member State that acted as 'rapporteur.'

Risk assessment reports of existing chemicals finalised in 2002		
SUBSTANCE	**CAS N>**	**Member State**
2-ethylhexyl acrylate	103-11-7	D
4'-tert-butyl-2',6'-dimethyl-3',5'-dinitroacetophenone	81-14-1	NL
5-tert-butyl-2,4,6-trinitro-m-xylene	81-15-2	NL
Benzene	71-43-2	D
Benzyl butyl phthalate	85-68-7	N
Cadmium	7440-43-9	B
Cadmium oxide	1306-19-0	B
Chloroacetic acid	79-11-8	NL
Perboric acid, sodium salt *	11138-47-9	A
Phenol *	108-95-2	D

** Human Health part of the report to be finalised in 2003.*

Main achievements in 2002 were:

- The discussions at the Technical Meeting on the risk assessment were finalised for 10 additional substances, bringing to a total of 76 the number of priority substances that have been risk assessed since the beginning of the ESR programme.
- The work area completed the preliminary screening of the IUCLID database for potential PBTs and vPvBs.
- 25 additional comprehensive EU Risk Assessment Reports were published on the Internet in 2002.
- Two Commission Regulations and three Commission Recommendations were published in 2002, for which the work area had carried out the preparatory work, provided the scientific justification and had prepared the draft texts.
- The Existing Substances Information System, a comprehensive tool for supplying information related to the Existing Substances Regulation went on-line in 2002.
- 2 training courses regarding IUCLID and the EU risk assessment procedures were carried out.

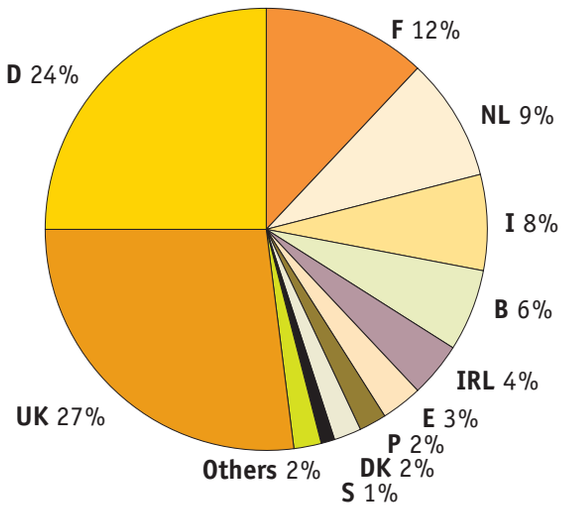
The notification and risk assessment of new chemicals

All new chemicals have to go through the notification (and risk assessment) process, as laid down in the Directives 67/548/EEC and 93/67/EEC.

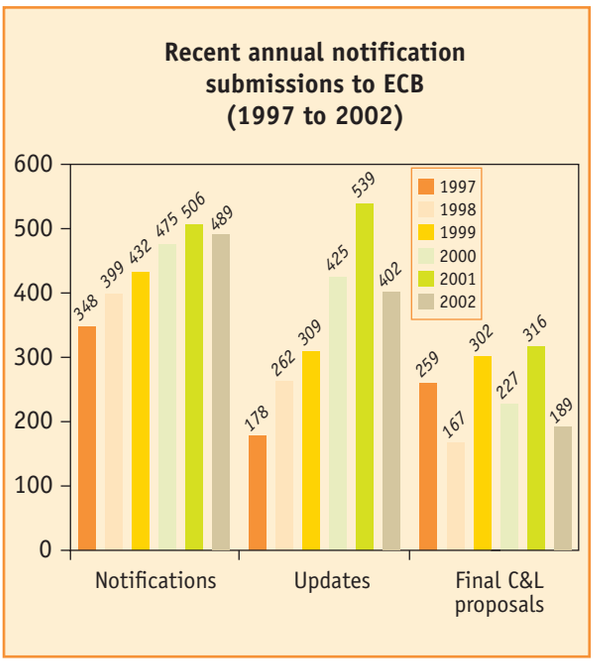
Over 5600 notifications in total, including over 3500 new chemical substances, have been submitted since 1983, currently an average of 400–450 notifications and 300–350 substances are processed per year. Irrespective of notification date, during the year 2002 somewhat fewer notifications were submitted to ECB, compared to the previous year and in contrary to a trend of steadily increasing numbers over several recent previous years.

Over half have been combined contributions from United Kingdom and Germany. Respecting substance origins, over half of new substances marketed in the EU during the year 2002 were foreign imports, principally from Japan, USA, and Switzerland. UK takes a primary role concerning imports with Germany representing a principal Member State for EU domestic manufacture.

About one third of notifications submitted since adoption of the 7th Amendment of the Directive are complete with risk assessment. No risk assessment is normally available for substances which are not classified (~30%) and for reduced notifications according Annex VIIC.



Cumulative notification contributions for new chemicals per Member State (1983-2002)



THE AUTHORIZATION OF BIOCIDES

Biocides are chemical preparations containing one or more active substances that are intended to control harmful organisms (such as pest control).

The Directive 98/8/EC concerning the placing of biocidal products on the market harmonizes the rules of such placement by introducing common data requirements for both active substances and biocidal products.

A first Review Regulation, Regulation (EC) No. 1896/2000 addressing the review of existing active substances was agreed on 7th September 2000, entering into force on 28th September 2000. This regulation gives a period for either notification of supported active substances or identification of non-supported active substances by 28th March 2002.

Regulation (EC) No. 1687/2002 was adopted on 25th September 2002, entering into force on 15th October 2002 giving an additional period until 31st January 2003 to notify active substances that have only been identified and to add product types to the already notified substances.

During 2002 the second review regulation, which is to phase out non-supported substances and inform about the order in which the product types are reviewed and give the rapporteur member states for the first 2 blocks of product types to be reviewed, was extensively discussed at CA level.

To prepare for the review programme the following tasks were undertaken in year 2002:

- The web page for biocides, **http://ecb.ei.jrc.it/biocides**, has continuously been updated, to enable industry to check that their information is registered correctly and to distribute information to third parties.
- The TNsG on Annex I, IA or IB Inclusion was finalised and placed on the web.
- The TNsG on Product Evaluation was finalised and placed on the web.
- The TNsG on Human Exposure to in Biocidal Products – Guidance on Exposure Estimation was finalised and placed on the web.
- The TNsG on Dossier Preparation and Study Evaluation was finalised and placed on the web.
- 3 IUCLID courses were successfully given to authorities of the member states, candidate countries and industry.
- The biocides team participated in numerous events and conferences aiming at explaining the Biocides Directive, the first review regulation and its consequences.
- The different technical guidance documents were further progressed; a second one on environmental emission scenarios for biocides was initiated.

THE INFORMATION EXCHANGE ON IMPORT AND EXPORT OF DANGEROUS SUBSTANCES

The ECB fulfils the duties of the Commission within the export notification process as laid down in Regulation 2455/92 by giving technical and scientific support for the implementation of the Regulation. The main issues of the Regulation are: to implement the EU export notification procedure; to make the voluntary UNEP/FAO Prior Informed Consent (PIC) procedure legally binding within the Community; and to use the same rules for classification, packaging and labelling outside the Community that apply in the internal market.

At the international level, a new regulation called the Rotterdam Convention was signed in September 1998, and is still in the process of ratification. The voluntary implementation of the Rotterdam Convention within the EU established the ECB as the central export notification authority on behalf of the Community. The European Database on EXport and Import of certain dangerous chemicals (EDEXIM) was modified to meet the new requirements during the interim period until the Convention will be legally binding.

All relevant Export Reference Numbers (ERNs) assigned within the EU export notification procedure, were published in the Official Journal twice during the year in all the official languages of the Community.

During 2002 a new regulation on Import/Export was being prepared to be in accordance with the requirements of the Rotterdam Convention.

The ECB continues to develop the National Profile Homepage in collaboration with the United Nations Institute for Training and Research (UNITAR). This Internet site has information on the existing national legal, institutional, administrative and technical infrastructure related to the sound management of chemicals for over 45 countries. The Internet address is: **http://www.unitar.org/cwm/nationalprofiles/index.htm**.

In addition, the ECB is actively supporting the development of several services within the INFOCAP project in the regime of the Intergovernmental Forum on Chemical Safety (IFCS). In 2002 the ECB has actively contributed to the two services of the INFOCAP by developing 4 internet sites for each service, allowing almost automanaged information systems according with the steering group indications.

RESEARCH ACTIVITIES

OMNIITOX project
(EC project number: G1RD – CT2001 – 00501)

The project OMNIITOX (Operational Models aNd Information tools for Industrial applications of eco/TOXicological impact assessments) aims to enhance the capability of industry to select more environmentally benign chemicals and processes. The project investigates refinement of environmental impact management for chemicals, incorporating Life Cycle Assessment (LCA) concepts. The approach has a comprehensive scope, beyond traditional substance specific RA, including web-based information retrieval. In collaboration with other partners, ECB leads a feasibility study of introducing elements and concepts of the LCA framework into the regulation of chemicals. The main activity in 2002 has been an LCA case study, comparing application of metal working fluids with and without chlorinated paraffins.

Review of EU Risk Assessment (RA) methodology for paper recycling

Risk Assessment (RA) for a new substance used as a solvent in carbonless copy paper has revealed uncertainties in the scenario of paper recycling. The RA has raised a wider issue concerning the validity of RA methodology relating to paper recycling. The project has undertaken to review this methodology by refining the RA for the new substance respective of paper recycling and through comparative survey of analogous RAs with this exposure scenario, available from notified substances registered in the new chemicals database (NCD).

A new JRC Activity on QSARs

Structure-activity relationships (SARs) and quantitative structure-activity relationships (QSARs), collectively referred to as (Q)SARS, are theoretical models that can be used to predict the physicochemical and biological properties of molecules. A SAR is a (qualitative) association between a chemical substructure and the potential of a chemical containing the substructure to exhibit a certain biological effect. A QSAR is a mathematical model that relates a quantitative measure of chemical structure (e.g. a physicochemical property) to a physical property or to a biological effect (e.g. a toxicological endpoint).

The general aim is to promote the development, validation and implementation of (Q)SARs that will be useful for regulatory purposes, in particular on the needs of the future EU legislation on chemicals (REACH system). The work is performed in close collaboration with ECVAM.

Another collaboration between ECB and ECVAM has been initiated on the evaluation of in vivo data on new substances relevant to development and validation on in vitro skin irritation assay, relating to R38 classification. Screening of notified substances registered in NCD allows selection of candidate substances for experimental study, and provides quality controlled in vivo data for comparative validation of alternative in vitro methods. Furthermore, similar activities to use data of the NCD were initiated with respect to teratogenicity and neurotoxicity.

SELECTED PUBLICATIONS 2002

BARAIBAR FENTANES J., COLE, T., NORAGER O., OLSSON, H., SOKULL-KLÜTTGEN, B., MARAS, K. (2002): *DES for Windows (version 6.1)* – Data entry screens for notification summaries on new chemical substances (Directive 67/548/EEC). Software to be obtained by ECB

COLE, T., OLSSON, H., SOKULL-KLÜTTGEN, B. (2002): *Manual of Decisions for implementation of the sixth and seventh amendments of Directive 67/548/EEC on dangerous substances* (Directives 79/831/EEC and 92/32/EEC). At http://ecb.jrc.it/new-chemicals/

The following publications regarding EU Risk Assessment on Existing Substances are available at http://ecb.jrc.it/existing-chemicals:

HANSEN, B.G., MUNN, S.J., DE BRUIJN, J., PAKALIN, S., LUOTAMO, M., BERTHAULT, F., VEGRO, S., HEIDORN, C.J.A., PELLEGRINI, G., VORMANN, K., ALLANOU, R., SCHEER, S., EDITORS (2002): *4-Nonylphenol (branched) and nonylphenol,* 2nd PL, Volume 10. EUR 20837 EN

HANSEN, B.G., MUNN, S.J., PAKALIN, S., HEIDORN, C.J.A., ALLANOU, R., SCHEER, S., PELLEGRINI, G., VEGRO, S., DE BRUIJN, J., LUOTAMO, M., VORMANN, K., LOONEN, H., BERTHAULT, F., PRADERIO, L., Editors (2002): *4-Choro-o-cresol,* 1st PL, Volume 11. EUR 19757 EN

HANSEN, B.G., MUNN, S.J., LUOTAMO, M., PAKALIN, S., BERTHAULT, F., DE BRUIJN, J., VEGRO, S., PELLEGRINI, G., ALLANOU, R., SCHEER, S., Editors (2002), Volume 12-15, 17:
Dimethyl Sulphate, 2nd PL, EUR 19838 EN
Ethyl acetoacetate, 1st PL, EUR 20396 EN
Dimethyldioctadecylammonium chloride, 1st PL, EUR 20397 EN
o-Anisidine, 2nd PL, EUR 19834 EN
Bis(pentabromophenyl) ether, 1st PL, EUR 20402 EN

HANSEN, B.G., MUNN, S.J., LUOTAMO, M., MUSSET, C., PAKALIN, S., DE BRUIJN, J., BERTHAULT, F., VEGRO, S., PELLEGRINI, G., ALLANOU, R., SCHEER, S., Editors (2002), Volume 18-25, 27:
Acetonitrile, 1st PL, EUR 19839 EN
Tert-Butyl methyl ether. 3rd PL, EUR 20417 EN
1,3-Butadiene, 1st PL, EUR 20420 EN
1,4-dioxane, 2nd PL, EUR 19833 EN
Methyl methacrylate, 1st PL, EUR 19832 EN
Methyloxirane, 2nd PL, EUR 20512 EN
Acrylamide, 1st PL, EUR 19835 EN
Methacrylic acid, 1st PL, EUR 19837 EN
Styrene (environment), 1st PL, EUR 20541 EN

HEIDORN, C. J. A., RASMUSSEN, K., HANSEN, B. G., NØRAGER, O., ALLANOU, R., SEYNAEVE, R., SCHEER, S., KAPPES, D. and BERNASCONI, R.: IUCLID: *An Information Management Tool for Existing Chemicals and Biocides. Accepted for publication in Journal of Chemical Information and Computer Sciences,* Dec. 2002

LAHANIATIS, M.R., PAKALIN, S. AND KETTRUP, A., *"Environmental and Human Health Risk Assessment"* in Fresenius Environmental Bulletin, Vol. 11, No. 10a, 713-735, 2002. ISSN 1018-4619

KAPPES, D. and RASMUSSEN, K.: *Progress on the Biocides Directive.* Accepted for publication in Pesticides Outlook, December 2002.

MUNN, S.J. AND HANSEN, B.G.: *"EU Risk Assessment: Science and Policy" in Toxicology*. In Print

RASMUSSEN, K. and KAPPES, D.: *Implementation of the Biocidal-Products-Directive: Technical Notes for Guidance in Support of Directive 98/8/EC*. Accepted for publication in Chimica Oggi, July 2002

RIEGO SINTES, J.; Editor (2002). *Guidance Document on the Determination of Particle Size Distribution, Fibre Length and Diameter Distribution of Chemical Substances*. Luxembourg: Office for Official Publications of the European Communities. EUR 20268 EN. ISBN 92-894-3704-9

RIEGO SINTES, Juan M.: *"La evaluación de las substancias químicas en la Unión Europea: Introducción a los métodos de ensayo"*, in: Repetto, M. editor, "Toxicología de Postgrado". Área de Toxicología. ISBN 84-699-6978-1. Universidad de Sevilla. CD-ROM. Sevilla 2002

SOKULL-KLÜTTGEN, B., COLE, T., JOHANSSON, S., OLSSON, H. (2002): *Notification of new chemical substances in accordance with Directive 67/548/EEC on the classification, packaging and labelling of dangerous substances - Technical Guidance for the completion of a summary notification dossier for a new chemical substance utilising the Structured Notification Interchange Format (SNIF)* - Base-set and levels 1 and 2.
At http://ecb.jrc.it/new-chemicals/

WEYERS, A., RÖMBKE, J., MOSER, T., RATTE, H.T. (2002): *Statistical Results and Implications of the Enchytraeid Reproduction Ringtest*. Env. Sci. Technol. 36 : 2116-2121

CONTACTS

Head of Unit
Gerald Vollmer
Tel.: +29 0332 789983
Fax: +39 0332 789963
gerald.vollmer@jrc.it

New Chemicals
Birgit Sokull-Kluettgen
Tel.: +39 0332 785849
Fax: +39 0332 789184
birgit.sokull-kluettgen@jrc.it

Existing Chemicals
Bjorn Hansen
Tel.: +39 0332 785884
Fax: +39 0332 789963
bjorn.hansen@jrc.it

Testing Methods
Juan Riego Sintes
Tel.: +39 0332 785987
Fax: +39 0332 789963
juan.riego-sintes@jrc.it

Classification and labeling & Export/Import
Elisabet Berggren
Tel.: +39 0332 789065
Fax: +39 0332 789963
elisabet.berggren@jrc.it

Ingrid Langezaal
Tel.: +39 0332 786135
Fax: +39 0332 789963
ingrid.langezaal@jrc.it

Biocides
Kirsten Rasmussen
Tel.: +39 0332 785344
Fax: +39 0332 789963
Kirsten.rasmussen@jrc.it

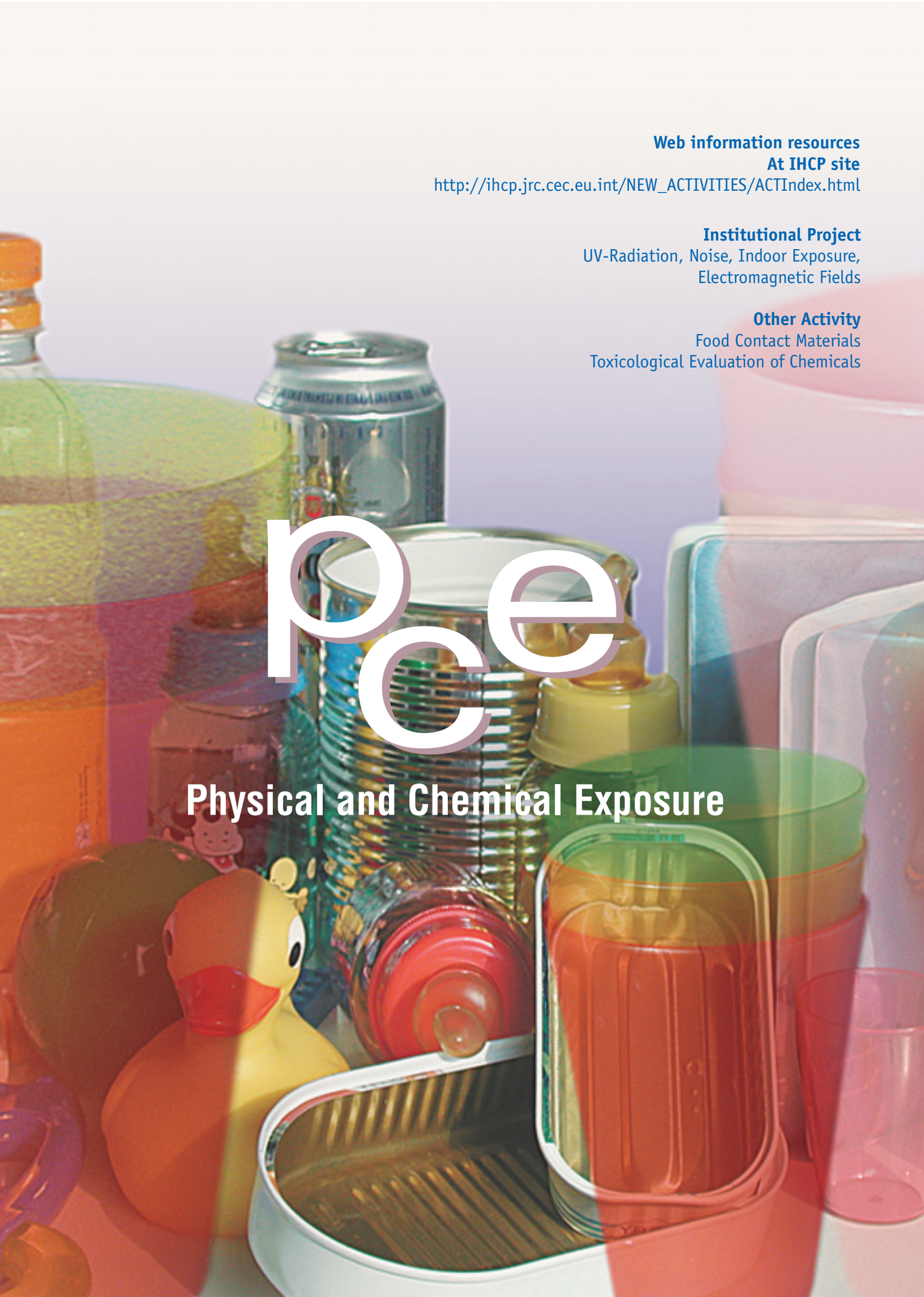
IUCLID database
Stefan Scheer
Tel.: +39 0332 785683
Fax: +39 0332 785862
Stefan.scheer@jrc.it

ECB Website
Remi Allanou
Tel.: +39 0332 786025
Fax: +39 0332 785862
remi.allanou@jrc.it

Web information resources
At IHCP site
http://ihcp.jrc.cec.eu.int/NEW_ACTIVITIES/ACTIndex.html

Institutional Project
UV-Radiation, Noise, Indoor Exposure,
Electromagnetic Fields

Other Activity
Food Contact Materials
Toxicological Evaluation of Chemicals



pce

Physical and Chemical Exposure

The mission of the Unit is to provide scientific understanding, information and assessment tools to support the Commission services in evaluating and quantifying human exposure and risk assessments for environmental stressors. Stressors include chemicals, biological contaminants, UV-radiation and noise.

As a result of the restructuring process, on 1st September 2001, the PCE Unit was transferred from the Institute for Environment and Sustainability (IES) to the Institute for Health and Consumer Protection (IHCP). The change was in close agreement with the overall mission of the Unit "to support the Commission Services in human exposure and risk assessment issues". Other sectors from IHCP joined the PCE Unit with the aim to combine efforts, in particular regarding the application of methods, of chemical/analytical and toxicological techniques, to improve human exposure and risk assessment for environmental stressors.

The UNIE-project (UV-radiation, Noise, Indoor Exposure, Electromagnetic Fields)

To accurately evaluate the health risk of European citizens from the exposure to environmental stressors, including chemicals, biological contaminants, UV-radiation and electromagnetic fields, the Commission requires sound scientific knowledge on occurrence, source strengths, dispersion and fate as well as reliable data on exposure of the population to these stressors.

Currently there is abundant evidence among experts and policy makers that human exposure data represent a major bottleneck in the risk assessment process. This has been recognised by the EU Council of the Environmental Ministers who requested the EU Commission to undertake action for eliminating existing deficiencies in exposure data.

In the frame of the UNIE project, a holistic approach is taken towards human exposure, including estimates and assessment of exposure due to the impact of chemical, biological and physical agents as the basis for the development and implementation of:

- Common measurement methods and protocols
- Common exposure models
- Exposure guidelines

Chemicals

During 2002 activities on chemicals mainly focussed to evaluate existing needs in exposure data, particularly on chemicals released from consumer products and articles. The overall scope was to create an operational platform for the analysis of the problem using available information from relevant partners, from the industry and scientific institutions and to define the way to fill in existing gaps. To this end, a workshop was organised on behalf of DG SANCO (17th June 2002) with the participation of all relevant stakeholders from industry, academia and international organisations and with the participation of decision and policy makers, with the aim to evaluate the current situation and to identify concrete policy needs. With the participation with DG SANCO, two main projects (EIS-CHEMRISKS and CHEMTEST) have been formulated and approved as European-wide networks to systematically exchange and assess information on emerging issues related to "Risks from chemicals released from consumer products and articles". The efforts of the PCE Unit on this subject will focus on filling the exposure gaps in a systematic, coherent manner, integrating current knowledge with novel state of the art approaches to determine and quantify the release of chemicals from products/articles. This work will substantially support the RAPEX notifications of the General Product Safety Directive and provide technical support to the relevant aspects of REACH in the frame of the New Chemicals Policy.

Tobacco Directive

One of the objectives of UNIE was to provide support (DG SANCO) for the implementation of the new Tobacco Directive, in particular, regarding the question of additives and pesticide residues in tobacco products. During 2002 various tobacco (cigarette) brands were analysed for their content in cations, anions, urea and pesticide residues. Emphasis was given to identifying and quantifying additives, e.g. ammonia released compounds (ammonium salts, urea), which might routinely be added to the tobacco used for cigarettes to increase as well as to control the delivery of nicotine to the respiratory tract of the smoker. Ammonia reacts with the indigenous nicotine salts and liberates free [base] nicotine. Ammonium concentrations in the investigated cigarette brands range from 0.07 to 0.49 g/100 g of tobacco. Urea has been found in three brands only, at levels between 6 and 20 mg/100 g.

The amount of pesticides appearing in mainstream smoke may vary from 10 to 20 % of the amount present in a cigarette. From the findings in our studies, it is estimated that up to 30 ng pesticides/cigarette can be taken up by the inhaling smoker. The daily intake of the most common pesticides (including the pesticides found in our studies) appearing in tobacco smoke by

the one-pack-per-day inhaling smoker amounts to ca. 0.75 µg/day.

The results obtained from the analysis of ten cigarette brands can be seen as preliminary. However, they clearly indicate the necessity for further investigations, as requested in the frame of the implementation of the new tobacco directive.

Inter-comparison of different types of passive samplers for volatile organic compounds (VOC)

In the last few years several types of passive (diffusion) samplers for volatile organic compounds have been made commercially available, and have been widely used for measurements in indoor and outdoor environments. However, hardly any data exist on the comparability of the various types of samplers. We have studied the sampling capacity of passive samplers for aromatic compounds (benzene, toluene, m/p-xylenes, o-xylene) under well-defined experimental conditions in the INDOORTRON facility (working concentrations: 50-60 µg/m^3 for benzene, toluene and o-xylene and 110-125 µg/m^3 for m/p-xylenes) and exposing them in the laboratory atmosphere for up to four weeks.

The following passive sampling devices were tested:

- Radiello I: (CS_2 elution)
- Radiello II carbograph : (thermal desorption)
- SKC: (CS_2 elution)
- Draeger ORSA: (CS_2 elution)
- Perkin Elmer: (thermal desorption)

Under the conditions in our study, preliminary evidence indicates that Radiello I, SKC and the Perkin Elmer passive samplers are better suited for the sampling of aromatic compounds. The average values obtained with the three aforementioned passive samplers show an overall variation of 10-15% of the default value, while for the other two samplers Radiello II and Draeger ORSA variations, which ranged for e.g. benzene from 20-50% of the default value, were measured. Experiments will be continued, under various conditions of temperature and humidity, including other groups of compounds (aliphatic, olefins).

Photo-induced degradation of gaseous pollutants on photo-catalytic surfaces containing titanium dioxide (PICADA)

The photo-catalytic properties of TiO_2 are well known since several years. Numerous studies report on the degradation of persistent organic compounds in e.g. water solutions when irradiated in the presence of TiO_2. In the frame of the project PICADA the photo-catalytic activity of TiO_2, added to different building materials, such as concrete, for the degradation of inorganic (NO, NO_2, O_3) and organic compounds (VOCs) has been tested. The experiments are carried out using the INDOORTRON facility and will be finalised during 2003. Preliminary results indicate high conversion rates (up to 60%) for, particularly, NO on TiO_2 surfaces.

Special exposure chamber positioned in the INDOORTRON for measuring the photo-induced degradation (UB-A) of gaseous pollutants on photo-catalytic surfaces containing TiO_2.

Harmonisation of indoor material emission labelling systems in the EU

A progress report has been issued on “Harmonisation of indoor materials emission labelling systems in the EU”. In this report a state of the art review of the existing labelling schemes in Europe has been performed, which has as outcome the classification of the different systems. Within this state of the art review all aspects of the different existing labelling systems have been elaborated. Besides the targeted compounds and analytical procedures, also aspects of quality assurance and economics, like market acceptance, have been taken into consideration. This progress report provides an overview of existing labels and also stresses the major objectives for further needs in harmonisation.

An interim report on “Establishing a database of outdoor and indoor CO source emissions and validating CO exposure data for the city of Milan” was prepared in the context of the development and validation of an urban air pollution micro-environmental exposure model.

European Collaborative Action (ECA): Urban Air, Indoor Environment and Human Exposure

For over 12 years the European Collaborative Action ECA "Indoor Air Quality & it's Impact on Man" has been implementing a multi-disciplinary collaboration of European scientists for healthy and environmentally sustainable buildings. The ECA has been hosted by the JRC/EI Air Quality Unit and managed by an independent scientific Steering Committee. In order to establish a

more direct and mutually beneficial co-operation with the Integrated Air Quality assessment (IAQA) programme, the ECA Steering Committee decided in 1999 to broaden its scope under a new title "Urban Air, Indoor Environment and Human Exposure". The focus of the renewed activity is urban and indoor air pollution exposure assessment, seen as part of environmental risk assessment and considering the needs of urban and indoor air quality management.

Specific examples of the working areas of ECA are: relative significance and assessment of urban outdoor and indoor sources of pollution, interaction between outdoor and indoor air quality of buildings, exposure to pollutants from the different outdoor and indoor sources in relation to health and comfort. By addressing such topics ECA will lay the ground for integrated air urban quality management to minimise exposures to air pollutants. It will thus continue to contribute to pre-normative research needed by EC services and national authorities responsible for preventing pollution and promoting health, comfort and quality of life.

UV Laboratory and ECUV (European Reference Centre for UV Radiation Measurements)

The UV laboratory provides support to specific policy actions on UV and hosts the European Reference Centre for UV Radiation Measurements (ECUV). A network for S&T reference of solar UV radiation measurements has been set up, which contributes towards the development of a total human exposure approach. The activity of the UV laboratory focuses on three topics:

- Solar UV radiation measurements
- Solar UV radiation surface modelling
- UV exposure and effects

Continuous measurements of total column ozone and solar UV irradiance using two Brewer spectrophotometers have been continued during the year 2002. The data have been reported to the UV networks, as there are the European projects (e.g. shared cost action project EDUCE), the WMO-GAW program and the World Ozone and UV Data Centre (WOUDC) in Toronto.

European Reference Centre for UV Radiation Measurements (ECUV): An international intercomparison has been successfully organised in the frame of the Shared Cost Action Project QASUME and in co-operation with the Renewable Energy Unit of the Institute for Environment and Sustainability (inter-institutional co-operation). Eight thoroughly checked spectroradiometers from six Member States (Austria, Finland, Germany, Greece, The Netherlands, United Kingdom and two instruments of ECUV participated at that intercomparison. One of these instruments (Brewer) is the JRC reference instrument on site and the other the transportable standard (Bentham) of ECUV. The spectroradiometer of the transportable unit was compared with all instruments participating at the intercomparison exercise to establish a relation, which would then be used as a reference for its calibration over the period of its regular operation at the European stations.

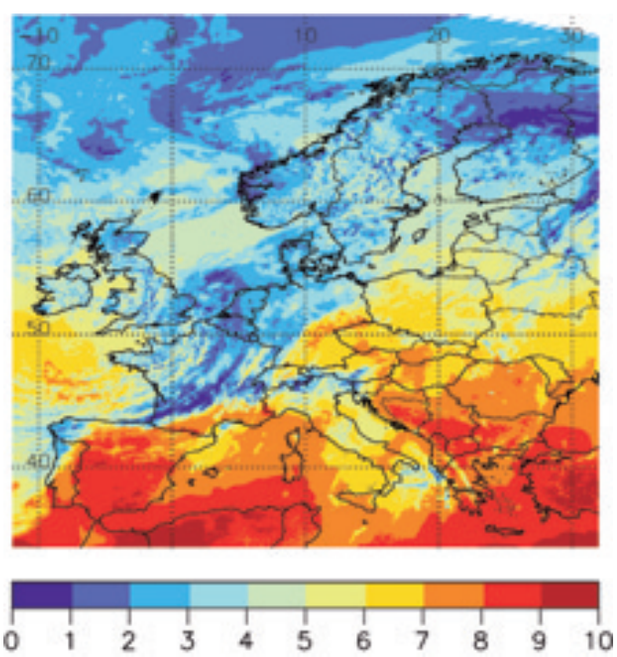
Different weather patterns varying from clear skies to heavy rain prevailed during the campaign, allowing the performance of the spectroradiometers to be evaluated under unfavourable conditions (as may be experienced at home sites) as well as the more desirable dry conditions. Measurements in the laboratory revealed that the calibration lamps of these instruments differ by up to 10%. Results of this campaign are presently being further evaluated.

The transportable standard started the first calibration round in June and until October on site calibrations with the JRC traveling standard have been performed at Innsbruck (A), Bilthoven (NL), Manchester (UK) and Helsinki (SF), Hannover (D) and Thessaloniki (GR). Additionally ECUV has been invited to participate during a measurement campaign organised by the European project INSPECTRO.

International intercomparison of solar UV radiometers.

Mapping of UV-B exposure for the last 15 years in Europe

The building of the European satellite-derived UV climatology has been systematically pursued. It consists in daily maps of UV radiation doses, covering the area from 34 to 74 N and 12E to 32E and from January 1984 to October 2002. At the end of 2002 only two winter months were still missing and the first version of the full data set should be completed by February 2003. Extracts of these maps have been provided to the partners in the project UVAC, studying the effects of climate on the population strength of the North East Atlantic cod. The satellite derived UV doses have been compared with the measurements at Ispra, with measurements at Tromsø and to higher resolution satellite derived maps produced by DLR (the latter two data sets being provided by UVAC partners). All comparisons are comforting with respect to the quality of the JRC climatology.



UV index on July 3rd 2002

Report on the inter-comparison of models for environmental noise

A report was prepared in which guidelines and prediction models for road traffic and railway noise used in the EU were compared on the basis of (a) full fact sheets, which were prepared and delivered by the EU MS and (b) computer software codes used for benchmark purposes.

Formulation and implementation of directives related to environmental noise

In the context of the HARMONOISE project ("Harmonised, Accurate and Reliable Methods for the EU Directive on the Assessment and Management of Environmental Noise") the 1st measurement campaign to collect noise & micrometeorological data, needed for the validation of the harmonised model under development, was prepared and successfully performed from 17 to 25 October 2002 in the La Crau (France).

Development, establishment and operation of a "European Information System on public health protection issues related to ElectroMagnetic Fields (EIS-EMF)"

The existing uncertainty in scientific information on the impact of electromagnetic fields and the subsequent contradictory interpretations from the scientific community fail to eliminate the sense of confusion pervasive among decision-makers. This is resulting in incoherent legal provisions or guidelines that perpetuate the insecurity felt by many Community citizens and undermines confidence in health protection authorities. During 2002 the IHCP/PCE Unit proposed the European Information System on EMF (EIS-EMF) project as a common basis for decision makers to increase the coherence of the approaches taken in the various Member States and help restore public confidence. This will systematically interface and compare information from various existing EIS at all levels (regional, national, international etc). In particular it will provide a European added value to international information channels, such as the WHO EMF project. The project has been approved and will be financially supported by DG SANCO in order to provide an EU wide risk communication on EMF based on improving the quality of available information and broadcasting it to European citizens. After a phase of consultations, it will be operational during 2003.

Toxicology

Major experimental activities in 2002 focused on the development of toxicogenomic approach in assessing the exposure to environmental chemicals and chemical mixtures. Studies were carried out applying DNA microarray techniques to assess gene expression modulation following exposure to chemical stressors. Results show that an exposure to arsenate in drinking water indicates a significant gene expression differential response in male and female tissues, supporting the different gender incidences in tumors as revealed by epidemiological studies on human populations exposed to drinking water arsenic.

Coordination activities in support to WHO-IPCS initiatives as member of the Steering Group on Endocrine Disrupting Chemical were concluded by the finalization of the Global Assessment Report, the implementation of the GEDRI database and the final report on Integrated Risk Assessment Approach.

BEVABS, European office for wine, alcohol and spirit drinks (Bureau Européen des Vins, Alcools et Boissons Spiritueuses)

In 2002 the institutional work of the BEVABS included aspects regarding training within the frame of its new official laboratories and quality control of isotopic measurements for wines. Transfer of know-how was carried out through a first specific training of a National Expert from Austria on preparation methods for isotopic and nuclear magnetic resonance (NMR) measurements on wine in October and November 2002. The monitoring of the performance of the official Member states Laboratories participating to the EU wine data bank continued through the FIT-Proficiency testing (Food analysis using Isotopic Techniques network- Proficiency Testing) which welcomed new participants from Slovenia and Hungary. Both countries have recently set up their own NMR and isotopic laboratories for wines, alcohol and agricultural products. Other activities on wines have been carried out on wines through the competitive research project GLYCEROL on development and testing methods for detection of adulteration of wine by illicit addition of glycerol. Also a new competitive project, WINE-DB started in May involving the network of laboratories of the EU Wine Data bank, and new partners from candidate countries (Hungary, Czech republic, Croatia and Romania). The scientific support to Commission DG and Member States official laboratories has been continued as regards official or new analytical methods and interpretation of corresponding results and by active scientific participation in key international bodies (e.g. OIV international office for wine and vine). Ad-hoc analyses for anti-fraud purposes have also been carried out in support to OLAF.

BEVABS has also continued to develop new methods applicable to detection of fraud, control of authenticity and verification of the origin of food and agricultural products. This has been achieved mainly through work carried out in competitive projects as for instance MEDEO in which methods based on NMR and isotopic techniques are developed and tested for detection of adulteration of olive oil. Similarly a new project, SPREADS, has been initiated for studying NMR measurements for detecting adulteration of spreadable fats. The same techniques have also been used in the project COFAWS which aims at developing analytical methods for verifying the origin of farmed and wild salmon and other fish.

Contact Materials

The Contact Materials Sector specialises in safety of chemicals regarding some consumer goods (i.e. toys), as well as food contact materials (FCM) in order to determine their safety and suitability for human use. In 2002 the European Commission has recommended the JRC-IHCP together with a European Network of FCM laboratories, as the future Community Reference Laboratory for FCM. The IHCP will continue to support policies toward assessment of human exposure with an emphasis on the development and harmonisation of methods.

Activities have included pre-normative research (migration into dry foods, active packaging, reaction products from jar sealants, release of chemicals from toys), monitoring of contaminants (from toys and in baby foods), and dissemination of information (organisation of two large conferences on recyclability and on scientific mobility, and one course of mathematic modeling). Activities have also included collaborative projects, ad-hoc tasks in support of CEN (European Committee for Standardisation) and representation in various expert groups for DG SANCO and DG ENTR. The activities in 2002 have resulted in two milestones: the designation of the contact materials laboratories as a future Community Reference Laboratory by DG SANCO, endorsed by the request of Member States to lead and co-ordinate an Official Network of Enforcement Laboratories. Another milestone has been the procedure of accreditation of the laboratory, which has resulted in an ISO 17025 Accreditation in January 2003. The systematic approach used in these tasks is directed not only towards the integration of the sector in the frame of risk assessment for consumer protection, but also to provide the scientific and technological tools to generate sound data and to promote the dissemination of both legislative and technical /scientific knowledge.

SELECTED PUBLICATIONS 2002

ALEU, J.; FRONZA, G.; FUGANTI, C.; SERRA, S.; BURKE, A.; GUILLOU, C. & RENIERO, F., "Differentiation of natural and synthetic phenylacetic acids by 2H-NMR of the derived benzoic acids" - *Eur. Food Res. Technol*. 2002, 214, 63

AROLA, ANTTI; KALLISKOTA, S.; DEN OUTER, P. N.; EDVARDSEN, K.; HANSEN, G.; KOSKELA, T.; MARTIN, T. J.; MATTHIJSEN, J.; MEERKOETTER, R.; PEETERS, P.; SECKMEYER, G.; SIMON, P. C.; SLAPER, H.; TAALAS, P.; VERDEBOUT, J., "Assessment of four methods to estimate surface UV radiation using satellite data, by comparison with ground measurements from four stations in Europe", *Journal of Geophysical Research Atmospheres,* August 28th 2002

BAIS, M.; BLUMTHALER, J.; GRÖBNER, G.; SECKMEYER, A.; R. WEBB; P. GORTS; T. KOSKELA; D. REMBGES; S. KAZADZIS; J. SCHREDER; P. COTTON; P. KELLY; N. KOUREMETI; K. RIKKONEN; H. STUDEMUND; R. TAX; S. WUTTKE, "Quality Assurance of Spectral Ultraviolet Measurements in Europe Through the Development of a Transportable Unit (QASUME)", (2002) Proceed. *SPIE,* 14-18 October, Shanghai, China

BRADLEY, E.; B. RAFFAEL; C. SIMONEAU, "Chemical migration into dry foodstuffs", *Drug, Cosmetics and Food Packaging,* March 2002

BRADLEY, E.; B. RAFFAEL; C. SIMONEAU, "Migration into dry foods", *Food Packaging Bulletin,* February 2002

BRESCIA, M. A.; DI MARTINO, G.; GUILLOU, C.; RENIERO, F.; SACCO, A.; SERRA, F. "Differentiation of geographical origin of durum wheat semolina samplesusing isotopic composition". *Rapid Communication in Mass Spectrometry* vol 16, issue 24, 2002 pp 2286-2290

BRUINEN DE BRUIN, Y.; O. HÄNNINEN; P. CARRER; M. MARONI; S. KEPHALOPOULOS; G. SCOTTO-DI-MARCO; M. JANTUNEN – "Simulation of urban population exposures to carbon monoxide using the EXPOLIS-MILAN microenvironment CO concentrations and time activity data" (submitted to the *Journal of Exposure Analysis and Environmental Epidemiology)*

BRUINEN DE BRUIN, Y.; P. CARRER; M. JANTUNEN; O. HÄNNINEN; G. SCOTTO DI MARCO; S. KEPHALOPOULOS; D. CAVALLO; M. MARONI – "Personal carbon monoxide exposure levels; contribution of local sources to exposures and micro-environmental concentrations in Milan" (submitted to the *Journal of Exposure Analysis and Environmental Epidemiology)*

CLAUSEN,G.; E. DE OLIVEIRA FERNANDES; W. DE GIDS; C. DELMOTTE; S.O. HANSSEN; S. KEPHALOPOULOS; M-C. LEMAIRE; T. LINDVALL; J.F. NICOL; M. SANTAMOURIS; O. SEPPÄNEN; V. J.M. VAN DEN BOGAARD; M. WILSON; P.WOUTERS - "Ventilation, good indoor air quality and rational use of energy", *ECA report* No. 24, 2002

DAMSTRA T. *et al.* (eds.) E. *Marafante part of the Scientific Expert group, Global Assessment of the State-of-the-Science of Endocrine Disruptors*. IPCS, WHO/PCS/EDC/02.2002

Estuarine Coastal & Shelf Science – 2002, Vol 54, 355

GRÖBNER, J.; D. REMBGES; A. BAIS; M. BLUMTHALER; T. CABOT; W. JOSEFSSON; T. KOSKELA; T. MORTEN; A. WEBB; U. WESTER, "Quality assurance of reference standards from nine European solar-ultraviolet monitoring laboratories" (2002), *Applied Optics,* 41, 4278-4282.

GRÖBNER, J.; A. BAIS; M. BLUMTHALER; T. CABOT; W. JOSEFSSON; T. KOSKELA; T. MORTEN; A. WEBB; U. WESTER; D. REMBGES; (2002) "Quality assurance of reference standards from nine European solar UV monitoring laboratories", *27th General Assembly EGS,* G. Res. Abs., 4, EGS02-A-03051

KEPHALOPOULOS, S. and KOTZIAS, D. – "Towards the development of harmonizednoise prediction methods in the EU", poster presented in the *11th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region,* Limassol, Cyprus, October 6th to 10th, 2001

KEPHALOPOULOS, S. co-author to ARVANITIS, A., BRUNO SPORTISSE, Ed., Book *Air Pollution Modelling and Simulation,* 2002

MOULA, M.; VERDEBOUT, J. and EVA, H., "Aerosol optical thickness retrieval over the Atlantic Ocean using GOES imager data", *Physics and Chemistry of the Earth,* 2002

MUNNS, W. R. Jr.; G. W. SUTER II; T. DAMSTRA; R. KROES; L. W. REITER; E. MARAFANTE, "Integrated risk assessment – Results of an international workshop". *Journal of Human and Ecological Risk Assessment,* Vol.9, No.1, 2003

NERÍN, C.; J. ALBIÑANA; M. R. PHILO; L. CASTLE; B. RAFFAEL and C. SIMONEAU, *Evaluation Of Some Screening Methods For The Analysis Of Contaminants In Recycled Pet Flakes, Food Additives and Contaminants,* in print

NEUBAUER, G.; D. PAPAMELETIOU; T. SAMARAS; Y. HAMNERIUS; J. WIART; K. LAMEDSCHWANDNER: "Methods to Assess Exposure of the population next to mobile communications base stations", *16th International Symposium on EMC* (URSI), Maastricht, August 2002

PAPAMELETIOU, D. (editor): Workshop Proceedings "Risks from chemicals released from consumer products/articles", JRC Ispra, June 2002

PAPAMELETIOU, D. and D. KOTZIAS: "Chemicals in Products/Articles: Strategy for an EU framework for human exposure data", EUREKA Conference EURO-SUSTAIN 2002, Rhodes 2-5 April 2002

PAPAMELETIOU, D.: "EMF-Risk perception and communication issues in the EU: The Role of the JRC Collaborative Action and of the European Information System on EMF (EIS-EMF)", Kick-off meeting of the JRC Collaborative Action on EMF, JRC, Ispra, March 1st, 2002

RAFFAEL, B., C. SIMONEAU, "Rapid screening of contaminants from PET bottles by headspace GC-MS". Journal of Chromatography (submitted)

SALIOT A.; DERIEUX S.; SADOUNI N.; BOULOUBASSI I.; FILLAUX J.; MOMZIKOFF A.; GONDRY G.; GUILLOU C.; BREAS O.; CAUWET G.; DELIAT G., "Characterization of particulate and dissolved organic matter supplied by river inputs and biological processes in the Danube delta and northwestern Black Sea mixing zone"

SIMONEAU, C.; G. ROEDER; E. ANKLAM, "Migration of Bisphenol A from baby bottles: effect of experimental conditions and European survey", *J. Agric. Food Chem*. (submitted)

SIMONEAU, C.; A. RONCARI; P. ZOCCHI; L. FANTONI, *Preparation and homogeneity testing of PVC toy materials for a European collaborative trial study on the migration of phthalates.* EUR technical report EUR (in print)

SIMONEAU, C.; A. RONCARI; P. ZOCCHI; P. HANNAERT; H. GEISS, *Applicability of the validated "head over heels" method to the measurement of all phthalates plasticisers from toys considered for ban.* EUR technical report EUR (in print)

SIMONEAU, C.; A. THEOBALD; P. RONCARI; P. HANNAERT and E. ANKLAM, "Time-temperature study of the kinetics of migration of BADGE (bisphenol-A- Diglycidyl-Ether) into fatty medium", *Food Additives and Contaminants* (2002), V19 Suppl.:73-78

SIMONEAU, C.; L. ROSSI, "Creation of on-line solutions in support of the dissemination of legislative and analytical information on food contact materials", *Food Additives and Contaminants,* (2002), V19 Suppl.: 201-208

THEOBALD, A.; A. RONCARI; C. SIMONEAU and E. ANKLAM, "Identification of epoxy containing migrants from can coatings in oil: A model study on reaction products of bisphenol-A-diglycidyl ether (BADGE) with solvents for coating production", *Deutsche Lebensmittel Rundschau* (2002), V98 N7:249-256

VERDEBOUT, J. co-author to the extended UV chapter of the Executive Summary of the *WMO/UNEP Scientific Assessment of Ozone Depletion 2002*. (official report for the Montreal Protocol).

WUTTKE S.; VERDEBOUT J. and SECKMEYER G., "An improved algorithm for satellite-derived UV radiation.", accepted for publication in *Photochemistry and Photobiology*

CONTACTS

Head of Unit
Dimitrios Kotzias
Tel.: +39 0332 789952
Fax: +39 0332 789453
Dimitrios.kotzias@jrc.it

Exposure Measurements and Risks of Chemicals
Demosthenes Papamelethiou / Dimitrios Kotzias
Tel.: +39 0332 789952
Fax: +39 0332 789453
Demosthenes.Papamelethiou@jrc.it

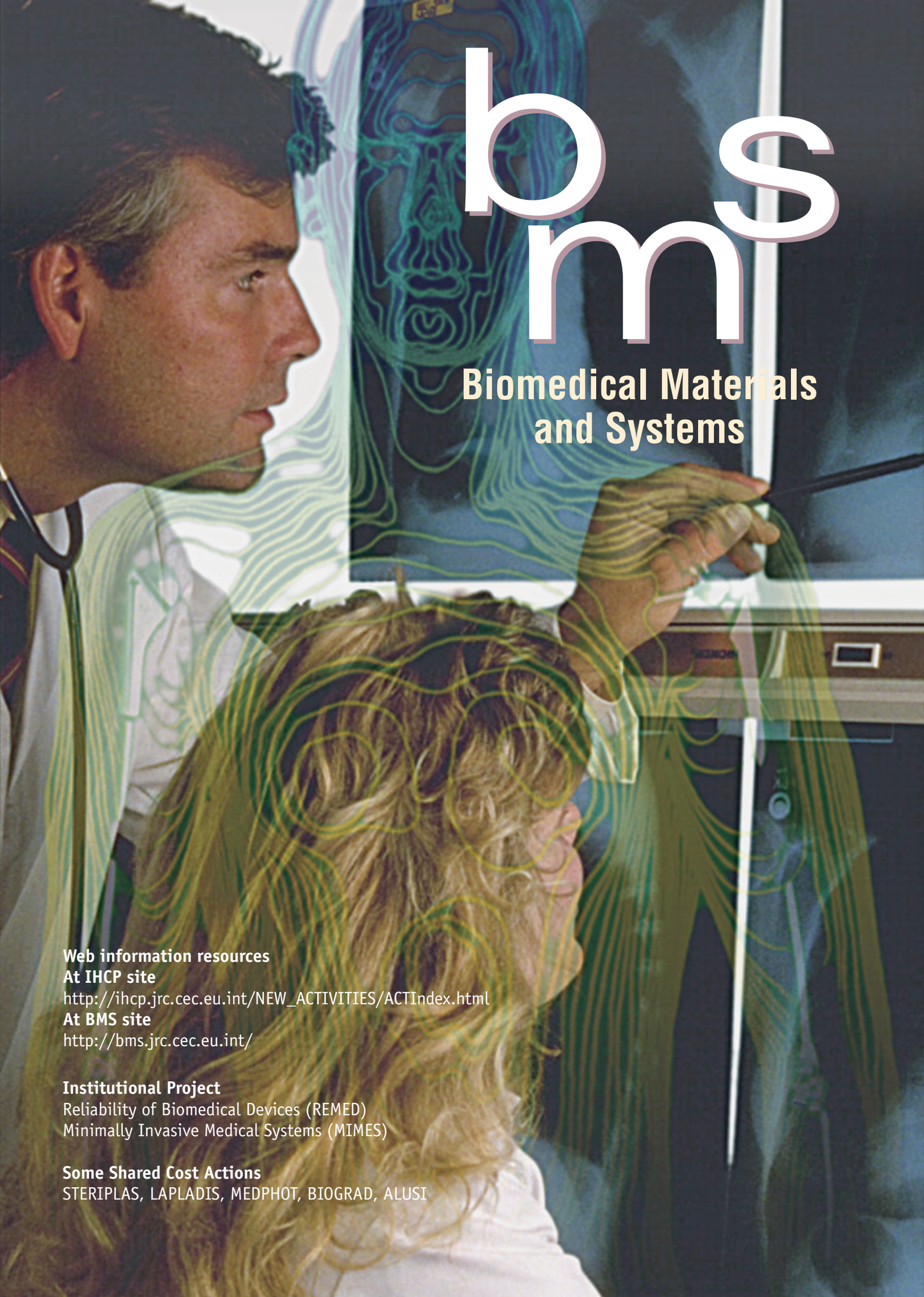
Exposure Modelling and Environmental Noise
Stylianos Kephalopoulos
Tel.: +39 0332 789871
Fax: +39 0332 785867
Stylianos.kephalopoulos@jrc.it

UV Laboratory / ECUV
Diana Rembges / Julian Groebner
Tel.: +39 0332 785953
Fax: +39 0332 785924
Diana.rembges@jrc.it

Toxicogenomics
Erminio Marafante / Libero Clerici
Tel:+39 0332 789144
Fax:+39 0332 786292
Erminio.marafante@jrc.it

BEVABS
Claude Guillou / Fabiano Reniero
Tel.: +39 0332 785678
Fax: +39 0332 789303
Claude.guillou@jrc.it

Contact Materials
Catherine Simoneau / Paola Piccinini
Tel.: +39 0332 785889
Fax: +39 0332 785707
Catherine.simoneau@jrc.it



bms

Biomedical Materials and Systems

Web information resources
At IHCP site
http://ihcp.jrc.cec.eu.int/NEW_ACTIVITIES/ACTIndex.html
At BMS site
http://bms.jrc.cec.eu.int/

Institutional Project
Reliability of Biomedical Devices (REMED)
Minimally Invasive Medical Systems (MIMES)

Some Shared Cost Actions
STERIPLAS, LAPLADIS, MEDPHOT, BIOGRAD, ALUSI

Biomedical Materials and Systems (BMS)

The Biomedical Materials and System (BMS) Unit develops, validates and uses advanced processing techniques and test methodologies for the qualification of biocompatible materials, medical devices, and diagnostic systems including medical applications of nuclear technology. The above focus is based on the demands of an ageing European population and consumer insistence on tools for early diagnosis and better planning of therapies. In particular, diagnostic tools that lead to the minimization of surgery are needed for improving patient care and cost effectiveness of public health care systems.

More specifically, the BMS activities in 2002 encompassed the following main priorities:

- **Reliability of Biomedical Devices (REMED)**: Activities in this priority area cover performance testing of biomedical devices in order to support the harmonization of testing methods for material release. This area also studies the performance of implant materials (orthopaedic and dental) and medical devices under clinically relevant conditions using a combination of advanced techniques (in support of Directive 93/42/EEC). It focuses on functional materials and systems, involving the development and characterization of biocompatible and bioactive surfaces in order to improve haemocompatibility of cardiovascular grafts, stents, catheters, and osteointegration of hip and knee replacement prostheses.
- **Minimally Invasive Medical Systems (MIMES)**: Activities in this area apply nuclear and optical imaging techniques to medical diagnosis and therapy. This involves, amongst other activities, the contribution to the development of standards for the distribution of radiotracers, as well as the participation in relevant European Networks

Both areas are of high relevance for maintaining quality health services, especially in view of demographic changes due to ageing of the population. The following sections will discuss in more detail the aforementioned priority areas and projects.

RELIABILITY OF BIOMEDICAL DEVICES (REMED)

Biomedical devices or implants, engineered from biomaterials, and designed to perform specific functions now play a major role in replacing or improving the function of every major body system and include dental implants and orthopaedic devices such as total knee and hip joint replacements, spinal implants or bone fixtures. From a regulatory point of view, acceptance of a wide range of medical devices at a European Level requires the validation and harmonization of testing and characterization methods for the systems and the materials used. The purpose of the project entitled "Reliability of Biomedical Devices" (REMED) is to provide The European Commission, in particular DG Enterprise and DG Health and Consumer Protection, with scientific and technical information related to the improvement of standards. In 2002 the main subjects of research were in the field of biomaterials processing and coatings, orthopaedic implant testing and advanced release testing methods for medical devices.

Biomaterials Processing and Coatings

Surfaces play a vital role in biology and medicine. Biological reactions are frequently described as occurring in the solution phase, but in fact most reaction in biology occur not in solution but at interfaces. A typical example of interfaces of biological importance is the cell surface/synthetic biomaterials. The advancements in surface science characterisation and modification techniques together with the advances in material science and molecular biology have significantly increase our ability to determine the surface composition and molecular structure of biomaterials.

This will result in the development of a biological model for surface science to obtain a detailed understanding of the role of surface properties of a material in controlling the biological reactivity. The challenge is to develop the biological model for surface science in the extreme complex and interactive in vivo biological environment.

Methods are being developed at the IHCP to study bio-film formation on materials used in medicine. The aim of the R&D program is to develop, assess and test plasma surface treatment for biomedical applications. In particular, our research is devoted to the deposition of carbon-based (DLC, nanocrystalline carbon, amorphous carbon nitride materials) for prosthetic applications and on the functionalisation of surfaces to improve properties such as adhesive bonding, wettability and biocompatibility. Carbon-based coatings, such as Diamond-like carbon (DLC) and

carbon nitride (CNx) coatings, have received attention in the recent years due to their hardness, wear resistance and low friction coefficient. These characteristics make carbon-based coatings interesting for applications in total joint replacement.

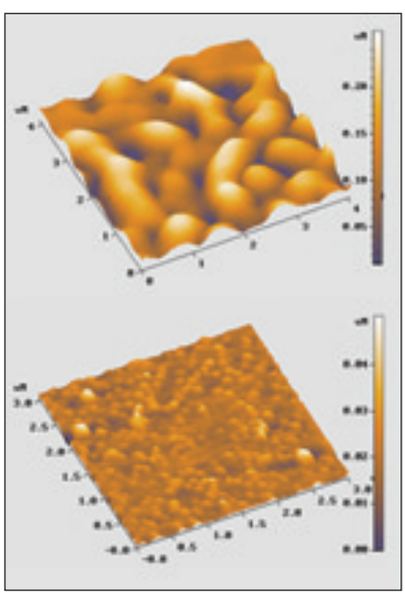
In 2002 the research activities focussing on the deposition of carbon thin films to improve mechanical properties of biomaterials, especially implants and prosthetic devices, by means of a Plasma Assisted Physical Vapour Deposition (PAPVD) reactor were continued. By coupling a microwave plasma source with two magnetron sources diamond-like carbon (DLC) films have been deposited with a controllable diamond character.

In 2002 the PAPVD method was also applied to deposit CNx films by using a carbon solid source coupled to a Distributed Electron Cyclotron Resonance (DECR) microwave plasma reactor. Optimizing the experimental conditions, films with hardness values up to 20 GPa have been achieved. Cellular studies were carried out at ECVAM, which demonstarted that the cells adhered well to the coated support showing the typical morphology of fibroblast growth in monolayers.

Research for improving materials biocompatibility was carried out by means of surface grafting via plasma treatments. This method allows to graft aldehyde, carboxylic or epoxy moieties on the surface and to covalently bond the antibodies through their amine functions. In 2002 functional films were produced by plasma polymerisation of acrylic acid (PPAA) vapour using an inductive and capacitive coupled plasma sources. X-ray Photoelectron Spectroscopy (XPS) and FTIR analyses of the coatings show that varying the process parameters (RF power, monomer flux), can control acrylic functions density on the surface and a thin film of up to 1000nm in thickness can be deposited with strong carboxylic character. Moreover, wetting studies indicate the possibility of tailoring surface physical properties (hydrophylicity-hydrophobicity) by adjusting the plasma parameters. These differences in physico-chemical surface properties strongly influence the biological response. For example, protein (HAS) attachment kinetics is strongly dependent on the plasma parameters with the highest amount of protein adhesion obtained at low RF power with the most hydrophylic film.

Another key issue studied in 2002 is the functionalization of surfaces to order and organise molecules and cells. Precision immobilization aims to imitate nature's way of organising molecules and represent an example of biomimetic strategy. Surface micro patterning is one of the methods used for controlling immobilization of biomolecules and cells both from chemical and topographic point of view. Polyethylene glycol (PEG) spin coated films have been masked and etched in a microwave plasma. Subsequently PPAA has been deposited in the obtained ridges. Samples were then cultured with endothelial CRL-1999 cells. Optical microscopy analysis demonstrated that cells tend to group in the functionalised PPAA stripes.

Another research field tackled during 2002 is related to the use plasma sources for sterilization of medical devices. This research is strictly related to a SCA project (STERIPLAS), in which a plasma process is used for the destruction of spores and pyrogens in medical devices and polymer treatments for pharmaceutical packaging. The RF and microwave sources available at JRC have been tested and compared for different gas mixtures (O2/Ar, H2/Ar, O2/H2 and N2/O2). Results show the joint effect of O radicals and UV emission from the discharge, on the sterilization rate of Bacillus Subtilis and a 6Log reduction can be obtained in 10 to 20 min depending on the conditions applied. The effects on polymers and organic thin films are used to identify different elemental mechanisms.



Above: Atomic Force Microscopy picture of proteins attachment on a Plasma Polymerised Acrylic Acid.
Below: Atomic Force Microscopy instrument used to study nano structured surfaces and protein interaction with polymers.

Orthopaedic Implant Testing Laboratory

Between 10% and 30% of the patients, who have received a joint prosthesis relying on a metal-polyethylene (UHMWPE) articulation, require a revision surgery already after approximately 10 years due to aseptic loosening of the implant. There is strong evidence that this loosening is caused by the accumulation of submicron sized wear debris in the periprosthetic tissue. These particulates interact with cells, in particular macrophages, causing a cascade of biological reactions. Thus, the main goal of research in improving the durability of orthopaedic implants is to reduce the number of wear debris released from the implants. For an effective improvement of prostheses, however, harmonized test methodologies are a pre-requisite.

The IHCP Orthopaedics Implant Testing Laboratory has therefore continued to focus its activities in 2002 on the improvement and harmonization of wear test methodologies in support to Directive 93/42/EEC including methods for the characterization of wear debris by SEM and quantitative image analysis. To complete its range of wear test facilities a state-of-the-art 6-station hip/knee simulator was installed, which enables the simulation of load and motion conditions representative for all types of patient activities such as walking and stair climbing.

These facilities were complimented with a novel horizontal pin-on-disk type wear tester, which is an in-house design that provides for a rapid and cost-effective wear screening of different types of medical grade polyethylene materials in a short period of time avoiding the need of long-term and expensive joint simulator tests. A collaboration contract with Politecnico di Milano has been initiated on the characterization of wear debris released from conventional and new types of crosslinked “zero wear” ultra-high molecular weight polyethylene (UHMWPE) articulating against CoCrMo counterfaces. Within the FP5-Shared Cost Action “ALUSI” newly developed types of wear couples consisting of alumina forming ferritic ODS alloys and UHMWPE were ranked according to the osteolytic potential of the released polyethylene wear debris. In the frame of the FP5 Shared Cost Action “BIOGRAD” screening wear tests a new methodology for screening wear tests of ceramic-ceramic wear couples based on the ASTM 732 Reciprocating-Pin-on-Flat Test has been successfully demonstrated.

Little is quantitatively known on fretting corrosion though recent clinical and experimental studies indicate that modular hip joint prosthesis, artificial knee joints and spinal fixators are prone to fretting corrosion damage. Therefore an exploratory research project has been initiated in 2002 supported through an individual Marie Curie Fellowship. It is the aim to develop a quantitative and precise methodology for fretting corrosion studies by combining radiotracer techniques with mechanical testing. By element-specific charged particle activation the release of certain ion species can be monitored online during fretting fatigue in body-like corrosive media. In 2002 a newly designed testing rig to study fretting corrosion effects on metal-ion release of Morse taper joints in modular design hip joint prosthesis has been set-up. First studies will be conducted in 2003 to simulate the release from the spherical head (CoCrMo) and the stem (CoNiCrMo or Ti6Al4V).

Advanced Release Testing Methods for Medical Devices

Together with ECVAM the BMS Unit hosts the Marie Curie Training Site BIORAD, which aims at providing high-level interdisciplinary doctoral training in testing of biomaterials using radiotracers. A key facility for this Training Site is the IHCP Biocyclotron, which is a concept that includes an interdisciplinary team of scientists working in an infrastructure of a cyclotron, laboratories for both the safe handling of radioisotopes and their use in biological and toxicological studies. Furthermore, it provides also training on toxicity test methods for biomaterials, particularly metal toxicity. Apart from the Biocyclotron the Training Site provides a unique combination of facilities and expertise including radiotracer laboratories, cell culture laboratories and facilities for performance testing of medical devices. In 2002 the selection procedure for two students to start the activities in 2003 was finished.

MINIMALLY INVASIVE MEDICAL SYSTEMS (MIMES)

Minimally invasive diagnostic and therapeutic medical methods often have great advantages in terms of patient comfort, safety, time and cost. The BMS Unit is involved in several aspects of development of advanced optical systems and radioisotope techniques. These are of particular relevance in the fight against cancer. Another activity addressed within the MIMES project in 2002 is an exploratory biomechanics study of bone strength for osteoporosis research.

Radioisotope production technology

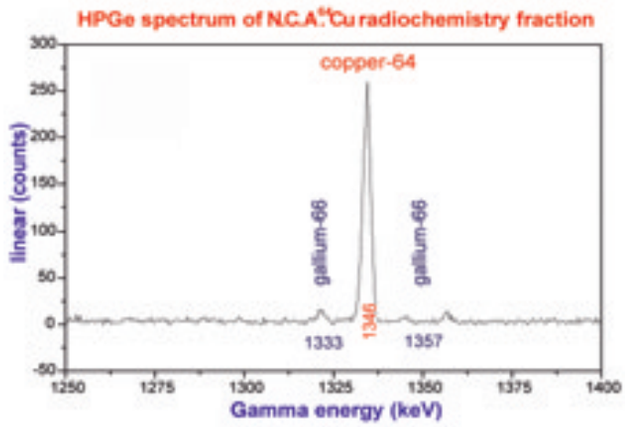
The IHCP biocyclotron allows the production of a vast variety of radioisotopes and is best suited for research into the production technology of radioisotopes for new medical applications. Radioisotopes can be used for labelling various kinds of molecules as biomedical radiotracers for diagnostic and therapeutic use. Such isotopic labelling allows the study of the functioning of the living body, from individual cells up to the entire organism. The obtained information is complementary to morphological anatomic information provided by x-ray or magnetic resonance techniques because it allows a functional imaging of body tissue e.g. to track down cancerous metastases, to early assess response to therapy or to detect cardiac disorder. Radiotracer studies can and help to understand the working of the brain and its alteration due to Alzheimer's or Parkinson's disease. Therefore, new types of radiotracers become increasingly important for the development and assessment of new therapeutic approaches.

Positron Emission Tomography (PET), the most advanced nuclear imaging technique, is gaining more and more attention as a tool for diagnosis and staging of cancer and has entered clinical practice in several European countries. All clinically relevant applications require short-lived, positron-emitting isotopes, which can only be produced by accelerators such as cyclotrons. IHCP responds to these demands by collaboration with industry and networking with other research groups.

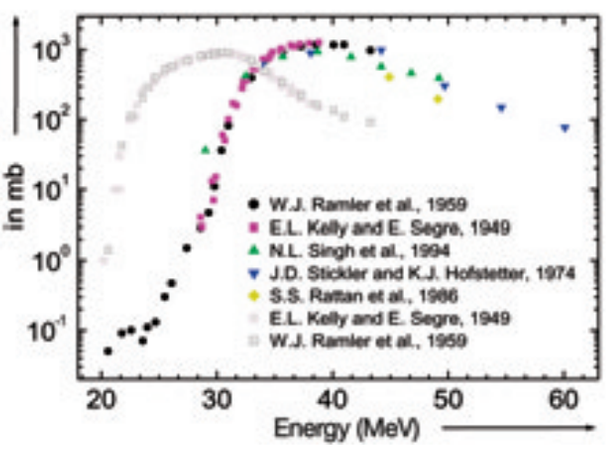
The establishment of a radiopharmaceutical laboratory for the production of [^{18}F] FDG (2-deoxy-2[^{18}F]-fluoro-D-glucose) in compliance with GMP (Good Manufacturing Practice) standards has been completed in 2002 in collaboration with an industrial partner. Extensive testing of the production process and the quality control procedures were carried out and the conditions were established for the daily "just-in-time" production of ^{18}F. The routine production of [^{18}F] FDG will be done in collaboration with a commercial partner. The collaboration aims at acquiring practical knowledge in the field of quality control at all stages of the production process as well as on the technical and logistic issues of distribution and delivery of short-lived radioisotopes to hospitals and research organisations from a central production site. This knowledge is of strategic importance, given the lack of Europe-wide regulations for the production and distribution of short-lived PET radiopharmaceuticals, which hinders the equal access of European citizen to the best possible health care services. Moreover, the experience gained in this collaboration will be valuable for initiatives in EU candidate states to assure supply of their population with short-lived radioisotopes of high quality.

In 2002 new results have been presented on alternative production routes for ^{64}Cu. This research project is collaboration with the Istituto Nazionale per la Fisica Nucleare at Milan. The scope of the project is to study a new method for the production of ^{64}Cu, which emits both positrons (b+) and electrons (b-). As a b-emitter ^{64}Cu has a potential application in cancer therapy and as a positron emitter the bio-distribution of a ^{64}Cu-labelled therapeutic molecule can simultaneously be imaged by PET. The new production route is based on deuteron irradiation of natural Zn and Zn enriched with ^{64}Zn. The study showed also an alternative route for the production of ^{67}Ga that is already used in nuclear medicine.

Work on the cyclotron in July 2002 (left) and one of the fully automatic synthesis modules for the production of [^{18}F] FDG (2-deoxy-2[^{18}F]-fluoro-D-glucose) in the radio-pharmaceutical laboratory (right).



A γ-spectrum of the Cu fraction after radiochemical processing of a Zn target. The γ-peak of the ^{64}Cu is well visible in spite of its very low branching ratio. The radiochemical separation procedures to eliminate the Ga impurities are currently improved.



Experimental reaction-cross sections for the production of ^{211}At and ^{210}At by bombarding ^{209}Bi with α-particles

The radioisotope ^{211}At is a α-particle emitter with interesting properties for cancer therapy. Its availability is however limited because cyclotrons are required for its production that are capable of creating a-particle beams with high intensity and an energy of at least 28 MeV. The MC40 biocyclotron at Ispra is one of the few machines with this capability in Europe. In 2002 theoretical calculations have been performed confirming the experimental reaction cross-section data. The results showed the necessity of new approaches in target development in order to achieve the theoretical yield and to enable production of clinically relevant batches of ^{211}At.

Optical Methods

There is a wide variety of methods of medical diagnosis or monitoring using optical techniques. These methods are all either non-invasive, or 'minimally-invasive', and several represent 'frontier' research, holding great potential to revolutionise medical diagnosis especially in the area of cancer detection. The BMS has a very active group with considerable knowledge and expertise in this field, which is likely to become of great importance in medicine and could involve future policy actions in terms of regulation and standardization in this highly innovative area. The main thrust of the work is in developing and testing of fibre-optic based sensors for monitoring physiological parameters such as temperature and pressure in clinical environments, and on the development of endoscopic techniques for cancer detection via advanced fluorescence imaging spectroscopy.

The past year saw further development of Bragg-grating and intensity-modulation fibre-optic sensors. Two JRC patents have already resulted from this work over the past few years and there is considerable interest from industrial and clinical partners to continue this development. In fact, clinical trials of a distributed temperature sensor for use in cancer therapy are planned. The sensors may be used for in-vivo temperature or pressure monitoring and for biochemical analysis for diagnostic purposes. Their main advantages are that they are non-metallic (thus may be used in EM-diagnostic environments such as NMR or MRI scanners), they are very biocompatible, easily sterilised and are completely passive (i.e. require no electrical power). In addition they are stable and cheap (therefore disposable). Progress has been made in refinement of the Bragg-grating writing facility, development of numerical models for fibre-optic gratings, development of opto-electronic demodulation systems, a study of the feasibility of using plastic optical fibres rather than glass fibres, and sensor system prototyping. Additionally studies have been made on the use of waveguides for measuring protein attachment on surface-modified polymers, and the use of spectroscopic sensors for detection of micotoxins. The former application will form the basis of new developments in the coming years.

In-vivo fluorescence-based tissue diagnosis is a technique that is receiving great interest and funding in many medical research institutions. A great deal of work needs to be done in terms of studying the optical characteristics of healthy and diseased tissue, and developing appropriate image processing techniques for clinical representation. Application of the technique via endoscopic imaging is being actively developed and many clinical trials have been made in different research centres. As a result of recent work, a JRC patent has been granted on a particular method of endoscopic fluorescence imaging, and further development and tests of a

prototype system have been made. The endoscopic system is undergoing performance tests and optimisation, and initial clinical trials are planned after the performance has been fully assessed using standard chromophores and cell cultures.

Biomechanical studies of calcified tissues

Osteoporosis is a disease that causes widespread suffering particularly in the elderly female population, and costs annually several billion Euro to health care systems in the EU. Osteoporosis incidence is predicted to rise dramatically over the coming decades, and yet there is still little or no policy progress to address this issue. A technical assessment study of areas of expertise of the BMS Unit relevant for osteoporosis research, highlighted several areas, one of which was nanomechanical testing of bone matrix tissue. Bone is a highly complex material, consisting of a composite architecture of collagen, hydroxyapatite and several cell types. An enormously intricate channelling system allows nutrients to be distributed throughout the bone, and a sensing system to operate that ensures that the bone architecture is constantly adapting itself to its mechanical environment. Non-invasive assessment of bone density is the main aim of current diagnostic systems for osteoporosis. These are based on X-ray absorption or ultrasonic techniques, the bone mineral density being correlated to some extent with bone strength. More advanced diagnostic techniques based on assessment of bone architecture are under development, and several research centres around the World are developing complex computer methods to simulate the mechanical response of the bone architecture to stress.

The aim of the current study is both to provide well-defined input to such models and, perhaps more importantly, to assess whether the use of anti-resorptive drugs has a significant effect on the mechanical properties of the bone tissue. Initial tests have been made on a variety of animal tissues, and it is planned this year to begin tests on samples derived from osteoporotic and healthy human tissue. Complementary to these initiatives the BMS takes part in a Consultation Panel of a European Union Policy Project, aiming to stimulate appropriate policy development as regards osteoporosis. Together with members of the Consultation Panel of this project and members of the International Osteoporosis Foundation an initiative has been taken to set up a project aiming at a “fragility fracture database” in the frame of the DG SANCO action programme for improving Health Information Systems.

SELECTED PUBLICATIONS 2002

GIBSON, P.N., STAMM, H. *The Use of Alloys in Prosthetic Devices. Business Briefing: Medical Device Manufacturing & Technology 2002,* June 2002, 48-51, World Markets Research Centre Ltd. Publs.

GIBSON, P.N. *X-Ray Structural Analysis Techniques, In monograph: Surface and Thin Film Analysis: A Compendium of Principles, Instrumentation and Applications,* Edited by H. Bubert and H. Jenett, Wiley-VCH Verlag GmbH, 2002, ISBN 3-527-30458-4

WHELAN, M.P., BOUHIFD, M. *Fluorescence Imaging Spectroscopy for in vivo Diagnosis of Pancreatic Disease. Biophotonics European Workshop,* FORTH-IESL, Univ. Crete, 18-19 October 2002, Heraklion, Crete (GR)

WHELAN, M.P., ALBRECHT, D.J. *Principles of Optical Fibre Bragg Sensors and their Application in Structural Monitoring*. In: Proceedings of the MACSI-NET Workshop, Politecnico, 20-22 November 2002, Milano (I)

NOSENZO, G., WHELAN, M.P., DALTON, T. *Condition Monitoring of Vibrating Composite Structures Based on Optical Fibre Strain Sensing and Finite Element Model Updating.* In: Proceedings of the Intern. Symposium "Smart Structures and Materials", SPIE, 17 - 21 March 2002, San Diego, Ca. (USA)

GARCIA-ALONSO, M.C., MACCHI, G., BRUGNONI, C. and STROOSNIJDER, M.F.: "Electrochemical release testing of a stainless steel in a glucose solution using thin layer activation", *Corrosion Science* 44 (2002) 129-143.

STROOSNIJDER M.F., HOFFMANN M., SAUVAGE T., BLONDIAUX G. Wear Evaluation of Cross-linked UHMWPE by Thin Layer Activation compared to Gravimetry, presented at the 28th. Society for Biomaterials Annual Meeting, Tampa, USA, April 24-27, 2002. Proceedings paper 286, Society for Biomaterials, Minneapolis, USA, 2002

R. SONNLEITNER, K. SPIRADEK-HAHN AND F. ROSSI, Microstructure of plasma nitrided layers on Aluminium. *Surf. and Coat. Technol.* 156 (2002) 149-154

P. COLPO, T. MEZIANI, P. SAUVAGEOT, G. CECCONE, N. GIBSON AND F. ROSSI; W and WC layers deposition by shielded inductively coupled plasma source. J. *Vac. Sci. Technol*. A20(5) 2002 1632-1638

P. ROSSINI, P. COLPO, G. CECCONE, K.D. JANDT AND F. ROSSI Surfaces engineering of polymeric films for biomedical applications, Materials Science and Engineering C 1050 (2002) 1 –6

CONTACTS

Head of Unit
Hermann Stamm
Tel.: +39 0332-789030
Fax: +39 0332-785388
hermann.stamm@jrc.it

Reliability of Biomedical Devices
Francois Rossi
Tel.: +39 0332-785443
Fax: +39 0332-789169
francois.rossi@jrc.it

Minimally Invasive Medical Systems (MIMES)
Neil Gibson
Tel.: +39 0332-785616
Fax: +39 0332-785036
neil.gibson@jrc.it

Uwe Holzwarth
Tel.: +39 0332-785194
Fax: +39 0332-789385
uwe.holzwarth@jrc.it

Support to Pharmaceutical Research

Web information resources
At IHCP site
http://ihcp.jrc.cec.eu.int/Activities/ACTPhar/ACTPhar.html

Institutional Projects
Telematic system for the EU pharmaceutical regulatory activity (ETOMEP)

Other Activity (through DG Enterprise)
EudraNet Services

The SPR has developed several complementary information and communication systems aiming at assisting the access to the authorised information on medicinal products throughout the EU regulatory authorities. In particular:

- The **EudraNet Services** supporting the cooperation for the entire EU market and post marketing surveillance (Eudra = European Union Drug Regulatory Authorities)
- The **EudraNet System** supporting the marketing authorisation process of medicinal products through the mutual recognition procedure enforced by the Council Regulation (EEC) No. 2309/93 and by Directive 2001/82/EC and Directive 2001/83/EC

Both EudraNet Services and the EudraTrack System have been operational since 1997. During 2002 SPR has finalized the transfer of the EudraNet Services to the EMEA (European Medicinal Evaluation Agency) and has transferred the services of the EudraTrack System to the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany) regulatory authority.

The following sections will discuss in more detail the two ICT systems supported by the SPR Unit in 2002.

EUDRANET SERVICES

EudraNet is a telecommunications network that has been established back in 1997 to facilitate the cooperative regulatory process in pharmaceuticals among the European Competent Authorities, the European Commission and the EMEA. The four objectives of the EudraNet services are:

- Enabling electronic communication and sharing of information between the European Commission, the EMEA, and the national competent authorities in pharmaceuticals.
- Providing a gateway for the secure and managed communication over the Internet between European administrations and pharmaceutical companies.
- Hosting and providing access to Community databases in pharmaceuticals.
- Providing a collaborative group working environment.

More specifically, EudraNet provides network services, application services (common databases) and support services.

The network consists of a backbone connecting dedicated lines of 32 organisations: the Commission, the EMEA and the national Competent authorities responsible for human and veterinary medicinal products in the EU, Norway and Iceland.

In 2002 in view of the transfer to the EMEA of all EudraNet activities, including both Eudra services and the Eudra network, the SPR undertook a major re-engineering and restructuring process to streamline and consolidate all activities and systems necessary to run EudraNet.

The network consolidation process involved a major upgrade of all systems and the EudraMail relay services and included also the migration to a new ISP, in line with the Commission framework contract. The overall security of the Eudra systems was also reviewed and new monitoring services were added to implement an Intrusion Detection System.

As part of the transfer activity, the EudraNet team in London, prepared a series of training sessions to facilitate the learning process for the new team in charge of the EudraNet services at the EMEA in addition to a detailed and thorough documentation on the systems. The training sessions, which included also introductory and tutoring components, were followed by hands-on sessions, where the systems were practically illustrated to the EMEA team.

The EMEA and the JRC signed the final EudraNet Services Transfer Agreement on December 30th 2002 with which the EudraNet equipment, the hardware on which the EudraNet runs and the commercial software used to implement Eudra services were officially transferred to EMEA.

EUDRATRACK SYSTEM

EudraTrack is a tracking system that permits the registration of procedures for marketing authorization submitted through the mutual recognition process to Competent Authorities in the Member States of the European Union. Data items relative to mutual recognition procedures are introduced by the reference and concerned Member States in a shared database that is available under controlled access to the EudraNet users. It provides a global picture of the ongoing procedures and statistical reports of those already accomplished. The reshaping of EudraTrack to prepare the transfer of the system to a new operator was continued in 2002. On July 3rd 2002 the European Competent Authorities indicated to the European Commission that the new operator is The Federal Institute for Drugs and Medical Devices of Germany (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM). The seven objectives of the transfer project were:

I. Automatizing the management operations of the EudraTrack system as well as the mutual index uploading procedure of the EudraTrack database.
II. Integrating the EudraTrack management tools and the EudraTrack web services to the EudraTrack software application version 5.3.9.
III. Testing the new hardware and software installation together with BfArM and DIMDI (Deutsche Institut für Medizinische Dokumentation und Information) before its shipment to DIMDI in September 2002.
IV. Continuing the help desk management operation and supporting the EudraTrack Sub-group chair requests until the system has been used as production at BfArM.
V. Uploading the data from the EudraTrack System database to the Mutual Recognition Product Index of the web site located in Sweden.
VI. Transferring the software source code files on one hand, and on the other hand, the data covering all procedures between October 1997 and December 13th 2002, user logins and their passwords of each competent authority and the history of login creation for each competent authority.
VII. Supporting fully the BfArM activities related to EudraTrack take over.

The services of the EudraTrack system were officially taken over by the BfArM on 16th December 2002.

SELECTED PUBLICATIONS 2002

RANA, A. - Medicine information network for Europe, *International Journal of Medical Marketing,* January 2002, vol. 2, no. 2, pp. 119-124

Contributing to the European Research Area

In January 2000 the European Commission proposed the creation of a **European Research Area** (COM (2000) 6). The main objective was to enhance the efficiency and innovative impact of Europe's research effort through better integration and co-ordination of research activities at a European level.

The IHCP has contributed to the implementation of a European Research Area (ERA) through scientific networking, the promotion of research training and mobility, and support to EU enlargement.

NETWORKS

The IHCP sought to network with EU Member States, Accession Countries, and Association countries with a view of co-ordinating research and exchange scientific and technical information:

- European Network of GMO Laboratories (ENGL)
- European thematic network on Optical Methods for Medical Diagnosis and Monitoring of Diseases (MEDPHOT)
- European thematic network on Innovative Plasma Technology for Societal Needs (PLASMATECH).

FACILITIES

The IHCP has a combination of facilities that have to be set up at the EU level. Some of these facilities are:

Biocyclotron
The Biocyclotron is a highly versatile particle accelerator with a rather large energy range and the capability of accelerating protons and alpha particles (up to energies of 40MeV) as well as deuterons (up to 20MeV). With this facility a wide variety of radioisotopes can be produced, making it especially suitable for research purposes.

Indoortron
The Indoortron laboratory is a unique, 30m^3 volume walk-in environmental chamber featuring controlled temperature, relative humidity, air quality, and air exchange rate.

BEVABS
BEVABS has a specialized laboratory that aims to ensure correct implementation of EU wine quality legislation.

RESEARCH TRAINING AND MOBILITY

The ERA promotes greater training and mobility of young and senior researchers as they play an important ole in the collaboration and networking of European research. Within this context, the IHCP hosted 55 collaborative staff including trainees, grant-holders (post-graduate and post-doc), visiting scientists, and seconded national experts.

SUPPORT TO EU ENLARGEMENT

The IHCP supports the adoption and implementation of EU legislation (*acquis communautaire*) in the Accession Countries through specialised enlargement activities (training and workshops):

- Two international workshops were organized by ECVAM in cooperation with institutions from Poland and Hungary on the Three Rs concept in relation to animal experimentation. The main aim of these workshops was to provide general information on the ethical and regulatory framework of the Three Rs concept and to learn about the implementation of Directive 86/609/EEC. In addition, the principles of validation and status of alternatives in the testing of chemicals, cosmetics, drugs, and biologicals were reviewed by named experts from EU Member States and CCs. In addition, two smaller workshops were held in Slovenia and the Czech Republic, which focused on specific topics, such as on alternatives to the use of animals in higher education and on the use of computer models as alternatives to animal experiments in chemical risk assessment.
- Two grant holders from CCs joined ECVAM to work on the development of structure-activity relationships for pharmacotoxicological endpoints and on the development of in vitro testing methods for assessment of neurotoxic and neurodegenerative potential, and a scientist from Poland was trained in a validated embryotoxicity test.
- BMS is a partner in an INTAS (International Association for the Promotion of Co-operation with Scientists from the New Independent States of the former Soviet Union) project in the field of plasma surface modification techniques for biomedical materials.

Prizes/Awards

- Enrico Sabbioni (ECVAM) received the 2002 Hevesy Medal award on 17th June in Antalya, Turkey, in recognition of his outstanding career contribution to radioanalytical chemistry, particularly in biomedical applications over 40-year period. The Hevesy Medal Award is the premier international award of excellence to honour outstanding achievements in radioanalytical and nuclear chemistry.
- The Young scientist prize for Scientific Innovation awarded to Maurice Whelan for his work on fluorescence spectroscopy and imaging and his development of a medical endoscope for the minimally invasive diagnosis of cancer and other chronic diseases.
- Janna Puumalainen, co-ordinator of the data mining and sampling project, received the JRC Young Scientist Award for Environmental Research in December 2002 and in addition, she received an award for the achievements in an international career by the Faculty of Forestry of the University of Joensuu, Finland, on the 11th October 2002.

Nominations

- Maurice Whelan was appointed to the Editorial Board of the Int. Journal *Strain*.
- Prof. Michael Balls (ECVAM) was appointed the Commander of the Most Excellent Order of the British Empire (CBE) in The Queen's Birthday Honours List for his services to humane animal research.

Patents (received by IHCP)

- Functionalization of stents with an enzyme capable of catabolizing cholesterol and lipids. EP Patent Application n.02292525.9.
- X-ray Reflectivity Apparatus and Method – a new dual-energy method aims to resolve difficulties experienced with standard experimental methods, opens up the possibility for rapid, non-destructive density measurements for modified surfaces and thin films. Patent Granted n.01934187.4-2204-GB0102441.
- "Detecting and mapping of inflamed zones in a living tissue". A medical diagnostic technique based on imaging fluorescence spectroscopy for the detection of early-stage disease such as cancer, without the need for taking a biopsy. Patent Granted, US 6,393,315 B1 (May 2002).
- "Luminous intensity sensor element and light modulating method and device employing such a sensor element". An adaptive optical device that can be used in the design of all-optical active devices, such as actively stabilised hyper-sensitive interferometric displacement sensors. Patent Granted, US 6,414,782 B1 (July 2002).

Training

- In 2002 two training courses on "The Analysis of Food Samples for the Presence of Genetically Modified Organisms" have been organised in collaboration with the Food Safety Programme within the European Centre for Environment and Health - Rome Division (ECR) of the World Health Organisation. The training courses are part of the collaborations between the two Institutions to promote food safety related issues in the WHO European Region, inside and beyond the actual EU borders, taking into special consideration EU Accession Countries, as well as Central and Eastern Countries with economies in transition. The training courses covered the areas i) DNA extraction from raw and processed materials, ii) screening of foodstuffs for the presence of GMOs by simple and nested PCR, iii) quantification of GMOs in ingredients by real-time PCR and iv) quantification of GMOs in ingredients by ELISA.
- Trainees came this time from Brazil, Croatia, Cuba, Cyprus, Czech Republic, Estonia, Germany, Greece, Hong Kong, Hungary, Italy, Lithuania, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, The Netherlands, United Kingdom, United States and Yugoslavia. In addition, The Agricultural Centre from Gödölö delegated one collaborator to both training sessions to learn how to train. A collaboration was initiated for a specific training programme destined to enlargement countries. Besides the training courses, the Biotechnology & GMOs Unit has offered individual training for specific needs. Training in this topic has been frequently requested due to its importance according to the increasing need to comply with current European legislative framework.
- The ECB organized 2 training courses regarding IUCLID and the EU risk assessment procedures and 3 IUCLID courses were successfully given to authorities of the member states, candidate countries and industry within ECB's activities on biocides.
- Apart from 2 large conferences on recyclability and on scientific mobility the PCE contact materials laboratories organized one course of mathematic modeling.
- The BIORAD Marie Curie Training Site was granted to the IHCP (ECVAM and BMS Biocylotron laboratories) aiming at high-level interdisciplinary doctoral training on biomaterials testing using radiotracers.
- For the training program of ECVAM see section "Support to Enlargement".

B&GMOs

ENTRANSFOOD

Aim:

Identification of key issues of the safety evaluation of genetically modified food crops.

Partners:

- RIKILT (NL), VBF (DK), UDUR.DBS (UK), CEA-Cad (F) EC JRC IHCP (I), IFA-Tulln (A), IFR (UK), RRI (UK), Unilever (UK), ISS (I), CEA-SPI (F), IEM (S), BIBRA (UK), TUM (D), Metapontum (I), LEI (NL), TNO (NL), KERKA (EL), SCRI (UK), RKI (D), ILSI (B), BgVV (D), Agre Vo (UK), IFT (D), EC JRC IRMM (B), BEUC (B), UKU (FIN), AHOLD (NL), Monsanto (B), Nestlé (CH), NVI (N)

QPCRGMOFOOD

Aim:

Development of reliable and transformation-event-specific tests for qualitative and quantitative detection of genetic modifications in food.

Partners:

- National Vet Inst (N), MATFORSK (N), INRA (F), DvP-CLO (B), LGC (UK), Gene-Scan (D), TERPAL-Danone (F), Unilever (NL), Bio-GEVES (F), DGCCRF (F), IFR (UK), CSIC (E)

ECVAM

NOVEL PYROGEN TESTS

Project Name: FP5 Project "Comparison and Validation of Novel Pyrogen Tests based on the Human Fever Reaction".

Aim:

To develop, evaluate and validate methods for the identification of pyrogens (fever inducing contaminants) in injectable drugs to replace the rabbit pyrogen test and the Limulus assay, both part of the European Pharmacopoeia requirements.

Partners:

- Steinbeis Transfer Centre For *In Vitro* Pharmacology and Toxicology at the University of Konstanz (G), NIBSC (UK), PEI (G), RIVM (NL), University of Innsbruck (A), University of Bern (CH), Novartis (CH), NIPH (NO), European Pharmacopoeia (F)

* **Shared-cost actions:** participation in shared-cost activities with other successful consortia.

PCE

WINE DB

Aim:

Establishing a wine data bank for analytical parameters for wines from third countries.

Partners:

- Bundesinstitut für gensundheitlichen Verbraucherschutz und Veterinärmedizin (D), Department for Environment, Food and Rural Affairs (UK), Eurofins (F), Vrije Universiteit (B), Ministry of Finance (CZ), Agronomical University and of Veterinary Medicine 'Ion Ionescu de la Brad' (RO), National Institute for Wine Qualification (HU), Croatian Institute of Viticulture and Enology (CR)

GLYCEROL

Aim:

To develop and test methods for detection of adulteration of wine by illicit addition of glycerol.

Partners:

- BfR - Bundesinstitut für Risikobewertung Berlin (D), Istituto San Michele all'Adige (I), Eurofins Analytics - Nantes (F), Central Science Laboratory-York (UK)

MEDEO

Aim:

To develop methods based on NMR and isotopic techniques and tested for detection of adulteration of olive oil.

Partners:

- Instituto de la Grasa (CSIC) Sevilla (E); Eurofins Analytics - Nantes (F); Central Science Laboratory- York (UK); CNR - Roma (I); Istituto Elaiotecnica Pescara (I); Stazione Sperimentale degli Oli e Grassi (SSOG)- Milano (I); National Hellenic Research Athens (GR)

COFAWS

Aim:

Confirmation of the origin of farmed and wild salmon and other fish.

Partners:

- Eurofins (F), Université de Nantes (F), North Atlantic Fisheries College (UK), SINTEF Fisheries and Aquaculture (SINTEFA) (NOR)

PICADA

Aim:

To test the photo-catalytic activity of TiO2, added to different building materials (concrete etc.) for its ability to induce degradation of inorganic (NO, NO2, O3) and organic compounds (VOCs).

Partners:

- Italcementi Group, Bergamo (I), University of Thessaloniki (GR)

UVAC

Aim:

Investigation on the Influence of UVR and Climate Conditions on Fish Stocks: A Case Study of the Northeast Arctic Cod.

Partners:

- Faculty of Fisheries and Natural Sciences, Bodø College (NOR); Technological Institute for Fisheries and Food, San Sebastián (E); Norwegian College of Fisheries Science, University of Tromsø (N); Norwegian Institute for Air Research, Tromsø (N); German Aerospace Center, Institute of Atmospheric Physica, Oberpfaffenhofen (D); Institute of Marine Science, Vigo (E)

FOODMIGROSURE

Aim:

To develop physico-chemical migration models of migration processes from plastics to real foodstuffs as a tool for estimation of consumer exposure from food contact materials.

Partners:

- Fraunhofer Institute of Process Engineering and Packaging, Freising (D), Central Science Laboratory, Dep. Food Environment & Rural Affairs, York (UK); FABES Forschungs GmbH für Analytik und Bewertung von Stoffübergängen (D); Pira International, Leatherhead (UK); University Santiago de Compostela, Dpto. Química Analitica, Nutrición y Bromatología of the Facultad de Farmacia (ES); Vienna University of Technology, Inst. Food Chemistry and Food Technology (A); Nestlé Research Center, Lausanne (CH); European Chemical Council; Bureaux International aux Techniques (BE)

INDEX

Aim:

To create a network of European scientists in the area of indoor air pollution and the herewith-associated health impacts.

Partners:

- Federal Environmental Agency Germany (UBA), National Institute for Health (KTL Kuopio, FIN), University of Aarhus (DK) (non-exhaustive list).

SPREADS

Aim:

To study NMR measurements for detection of adulteration of spreadable fats.

Partners:

- Universität für Bodenkultur (A), Bundesanstalt fur Milchforschung (D), Unilever Nederland BV (NL), Mylnefield Research Services LTD (UK)

EIS-EMF

Aim:

To set up a European Information System on public health protection issues related to Electromagnetic fields (EIS-EMF) as a common basis for decision makers to increase the coherence of the approaches taken in the various Member States and help restore public confidence.

Partner:

- Research Centre Seibersdorf (A)

GC-IRMS

Aim:

Feasibility study for establishment of reference materials for the gas chromatography isotopic ratio mass spectrometry.

Partners:

- Eurofins Analytics - Nantes (F), Central Science Laboratory- York (UK), INETI - Lisboa (P)

HARMONOISE

Aim:

To develop methods by which the sound power output and the directivity of sources of road and rail traffic can be described and assessed as an accurate physical quantity which is independent of short distance sound propagation, including establishment of a correlation with future legislation on limiting the noise generation, set up of data base.

Partners:

- AEA Technology Rail BV (SP), Swedish National Testing and Research Institute; Transport Research Laboratory (UK); VTI, Swedish Road and Transport Research Institute; Technical University of Gdansk, Autostrade (I).; TNO Institute of Applied Physics (NL) (non-exhaustive list)

QASUME

Aim:

The development of a new approach for facilitating Quality Assurance of solar ultraviolet spectral irradiance measurements presently carried out in Europe. In this frame a transportable Unit, developed and hosted at the PCE Unit, which, after thorough testing and validation, will be visiting European UV stations to acquire spectral measurements of global solar irradiance that will be compared with those of the local spectroradiometers

Partners:

- Laboratory of Atmospheric Physics, Aristotle University of Thessaloniki (GR), University of Innsbruck (A), University of Manchester Institute of Science & Technology (UK), Institute for Meteorology and Climatology, University of Hannover (D), National Institute for Public Health and the Environment (RIVM) (NL), Finnish Meteorological Institute (FIN).

EDUCE

Aim:

To investigate the ultraviolet (UV) radiation climate in Europe.

Partners:

- Institute for Meteorology and Climatology, University of Hannover (D); Norwegian University of Science and Technology; Institute for Geophysics, Astrophysics and Meteorology, University of Graz (A); Finnish Meteorological Institute; British Antarctic Survey; Laboratory of Atmospheric Physics, Aristotle University of Thessaloniki (GR); National Institute of Public Health and the Environment (NL); University of Manchester Institute of Science & Technology (UK); University of Innsbruck (A); Solar and Ozone Observatory - Czech Hydrometeorological Institute (CZ); Institute of Geophysics - Polish Academy of Sciences (PL); Tartu Observatory (Estonia); (non-exhaustive list)

BMS

EVIGeM (virtual Institute)

Aim:

The European Virtual Institute of Geometry Measurement (EVIGeM) consists of a linked group of European partners, committed to assists and help members and any external customer on all kind of problems concerning geometry measurements.

Partners:

- BIBA (D), Knapp (CH), Mahr (D), Unimetrik (E)

BIOGRAD

Aim:

Increasing the performance of total hip replacement prostheses through high functionally graded material innovation and design.

Partners:

- Lima Lto (I), Ceramtec (D), HIP Bodycote (UK)
- University of Leuven (B), Helsinki University of Technology (FI), LEMI (F), Josef Stefan Institute (SLO), Nuclear Physics Institute (CZ)

ALUSI

Aim:

Development of alumina forming ODS ferritic superalloys as new biomaterials for surgical implants.

Partners:

- Consejo Superior de Investigaciones Científicas (CSIC.CENIM) (SP), Asociación Instituto de Biomecánica de Valencia (SP), Istituto Ortopedico Rizzoli (I), Technische Universität Clausthal (D), Surgival (SP), Metallwerk Plansee GmbH (G)

STERIPLAS

Aim:

Study and validation of an advance plasma sterilisation process.

Partners:

- ARJO WIGGINS (F), R BOSCH GmbH (D), METAL PROCESS (F), BIOMATECH S.A. (F), C.I.R.M. (I)

LAPLADIS

Aim:

Large Area Plasma Etching Process for Display Applications.

Partners:

- FIAT (I), THOMSOM (F), FHR (D), EUROINKS (I)

IFCA

Aim:

Immunoprobes for Food Contamination Analysis (IFCA).

Partners:

- École Nationale Supérieure de Chimie de Paris (F), Universidad de Vigo (E), Innosense SpA (I), LCC (CH), Abkem (ES), CSMA (UK)

SPOTS

Aim:

Standardisation Project for Optical Techniques of Strain Measurement.

Partners:

- University of Sheffield (UK), Optical Metrology Innovations (IRL), Ettemeyer AG (D), NPL Management Ltd (UK), SNECMA Moteurs (F), Honlet Optical Systems GMBH (D), Politechnika Warszawska (PL), CRF Società Consortile per Azioni (I), Eidgenössische Materialprüfungs- und Forschungsanstalt (CH)

MEDPHOT

Aim:

Use of optical Methods for Medical Diagnosis and monitoring of diseases.

Partners:

- ISIS OPTRONICS GmbH (D), R. Wolf GmbH, STORZ (D)
- FORTH-ISEL (GR), PTB-National Metrology Institute of Germany, Lund Laser Centre (D)
- ILM-University of Ulm, Robert-Rossle Hospital-Berlin, Humboldt University, MLL-University, Lubeck (F), Storz (D)
- University L'Aquila (I), Univerity of Paris XIII (F), University of Twente (NL)
- AMC, Laser Centre (NL), Politecnico di Milano-POLIMI (I), Academisch Ziekenhuis Rotterdam (NL), ICSTM- Imperial College (UK)

European Commission

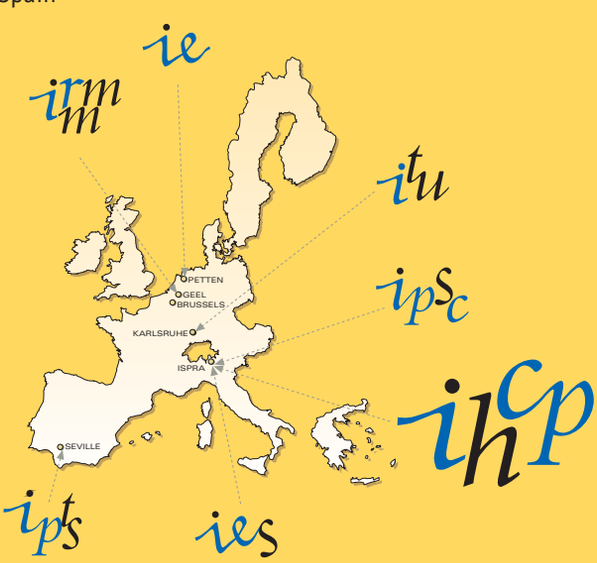
EUR Report 20660 EN – Institute for Health and Consumer Protection (IHCP) – Activity Report 2002
Editor: Michael Hoffmann
Luxembourg: Office for Official Publications of the European Communities
2003 – 64 pp. – 21.0 x 29.7 cm
Scientific and Technical Research series
ISBN 92-894-5312-5

JRC and the IHCP
http://www.jrc.org/

The Joint Research Centre (JRC) is a Directorate General (DG) of the European Commission. It has its headquarters in Brussels and seven institutes located in five separate sites:

- Institute for Reference Materials and Measurements (IRMM) — Geel, Belgium
- Institute for Transuranium Elements (ITU) — Karlsruhe, Germany
- Institute for Energy (IE) — Petten, The Netherlands
- Institute for Prospective Technological Studies (IPTS) — Seville, Spain

The largest site is located in Ispra, Italy, hosting three institutes:
- Institute for Health and Consumer Protection (IHCP)
- Institute for Environment and Sustainability (IES)
- Institute for the Protection and Security of the Citizen (IPSC)



LB-NA-20-660-EN-C

The mission of the Joint Research Centre is to provide customer-driven scientific and technical support for the conception, development, implementation and monitoring of European Union policies. As a service of the European Commission, the JRC functions as a reference centre of science and technology for the Community. Close to the policy-making process, it serves the common interest of the Member States, while being independent of commercial or national interests.

EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

ISBN 92-894-5312-5

9 789289 453127

Publications Office
Publications.eu.int